NICE National Institute for Health and Care Excellence

FAST TRACK APPRAISAL (FTA)

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Tofacitinib for treating active ankylosing spondylitis [ID3865]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company cost comparison** from Pfizer[1]

2. **Clarification letters**
   - Company response to NICE's request for clarification

3. **Patient group, professional group and NHS organisation submission** from:
   a. National Axial Spondyloarthritis Society
   b. British Society for Rheumatology (endorsed by the Royal College of Physicians)

4. **Expert personal perspectives** from:
   a. Clinical expert, nominated by British Society for Rheumatology
   b. Patient expert, nominated by National Axial Spondyloarthritis Society
   c. Patient expert, nominated by National Axial Spondyloarthritis Society

5. **Evidence Review Group report** prepared by York Centre for Reviews and Dissemination

6. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

[1] Please note that during the scrutiny process it was decided that the most appropriate comparators for tofacitinib in the FTA process were the IL-17 inhibitors, secukinumab and ixekizumab. As such the appropriate population is now the bDMARD experienced population. The original submission document has been included for information but all comparisons with and references to adalimumab or other TNF alpha inhibitors as comparators (in the submissions or model) are no longer part of the decision problem for this FTA.

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Fast track appraisal: cost-comparison case

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID3865 Tofacitinib for AS - DocumentB	**V0.1**	**Yes**	**30.11.2021**

Items below to be reviewed prior to submission

Completed before submission	Yes/ no
Contents, list of Tables and Figures updated	Yes
Table and Figure numbers updated	Yes
Full list of abbreviations/ acronyms	Yes
Abbreviations/ acronyms for Tables and Figures	Yes
Reference list updated	Yes
Reference pack highlighted and stored in the drives	Yes
All academically confidential information is highlighted in yellow and underlined in the electronic version sent to NICE	Yes
All commercially confidential information is highlighted in blue and underlined in the electronic version sent to NICE	Yes
Checklist of confidential information (provided by NICE with the invitation to submit) is completed and submitted	Yes
Bold content that points to further data in the appendices	Yes
An updated executable electronic copy of the economic model is included in the version sent to NICE, with full access to the programming code	Yes
Update proposed tofa indication throughout: "Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy."	Yes
Confirm that page limit (without NICE template pages) is 100 pages, "excluding the appendices and the pages covered by the template"	Yes

Contents

Tables and figures

Abbreviations

Abbreviation	Description
AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis QoL
AxSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath AS Metrology Index
bDMARD	Biologic disease-modifying anti-rheumatic drug
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSR	British Society for Rheumatology
CE	Cost-effectiveness
cfb	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran-Mantel Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COX	Cyclooxygenase-2
CrI	Credible interval
CRP	C-reactive protein
CTS	Clinical trial simulations
CV	Cardiovascular
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life Five Dimension
EQ-5D-3L	European Quality of Life Five Dimension Three Level Scale
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate

FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FBC	Full Blood Count
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effects
GCP	Good clinical practice (guidelines)
GP	General practitioner
HCHS	Hospital and community health services
HIV	Human Immunodeficiency Virus
HLA-B27	Human leukocyte antigen B27
HMSL	Hospital Marketing Services Ltd
HPA	Hospital pharmacy audit
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
hsCRP	High-sensitivity CRP
HTA	Health technology appraisal
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
IL-17	Interleukin-17A inhibitor
IV	Intravenous
JAK	Janus kinase
LFT	Liver function test
LOCF	Last Observation Carried Forward
MA	Marketing authorisation
MACE	Major adverse cardiovascular events
MAR	Missing at Random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimal important change
MRI	Magnetic resonance imaging
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
MTX	Methotrexate

NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NNH	Number needed to harm
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PGA	Patient's Global Assessment of Disease
PICOS	Population, Intervention, Comparator, Outcomes, Study
PP	Per protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic arthritis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised control trials
RE	Random effects
RWE	Real world evidence
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form health survey
SI	Sacroiliac
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
STAT	Signal transducer and activator of transcription
TA	Technical appraisal
TB	Tuberculosis
TEAE	Treatment emergent adverse event
THT	Tuberculosis test
TNF	Tumor necrosis factor
TNFi	TNF-alpha inhibitor

TSD	Technical support document
UC	Ulcerative colitis
U&E	Urea and electrolytes
UK	United Kingdom
VAS	Visual analogue scale
VTE	Venous thromboembolism

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

B.1.1.1 Population

The submission covers the technology's full anticipated marketing authorisation for this indication, namely adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

The submission covers the full population of the marketing authorisation.

B.1.1.2 Comparator

Conventional therapy for AS includes anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Alternative pharmacological management of AS includes biologic disease-modifying anti-rheumatic drugs (bDMARDs) to reduce the frequency, severity of and rate of disease progression. Currently, NICE recommends the following treatment options:

- **Treatment of AS using bDMARDs (TNF-alpha inhibitors [TNFis]) – adalimumab, certolizumab pegol, etanercept, golimumab and infliximab**
    - Adults with severe active AS that have responded inadequately to, or who cannot tolerate, conventional therapy (NSAIDs) are treated using adalimumab, etanercept, certolizumab pegol, infliximab or golimumab (1).
    - Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (2).
- **Treatment of AS using bDMARDs (IL-17A inhibitors) – secukinumab & ixekizumab**
    - Secukinumab is recommended, within its marketing authorisation, for treating active ankylosing spondylitis in adults whose disease has

responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors). Ixekizumab is recommended only if TNFis are not suitable or do not control the condition well enough (2-4).

- In UK clinical practice, the choice of treatment should be made following discussion between the clinician and the patient. This may include considering associated conditions such as extra articular manifestations, including uveitis, psoriasis, and inflammatory bowel disease (2-4).

Market share data for all recommended products and ongoing appraisals are included in Table 1 and are taken from IQVIA Hospital Pharmacy Audit (HPA; Hospital Dispensing) and IQVIA Hospital Marketing Services Ltd (HMSL; Patient Diary Study) datasets. The HPA dataset includes departmental dispensing data to help understand prescribing patterns with broad coverage across the UK. The HMSL dataset consists of a syndicated diary study of specialists, providing data on their relationships with patients and specialty prescribing patterns. The data are collected using consistent methodology, representing treatment for people diagnosed with axial spondyloarthritis (axSpA) from April 2017 to November 2020 (Table 1) (5). While the axSpa population includes patients with AS and non-radiographic axSpA, prescribing patterns are believed to be similar across both indications, as confirmed by a clinical expert. (6)

Table 1: UK Market Share for Treatments of patients with axSpA who had responded Inadequately to or who are Intolerant to NSAIDs

Period	Adalimumab	Certolizumab pegol	Secukinumab	Etanercept	Infliximab	Golimumab	Ixekizumab	Tofacitinib
Nov 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nov 2018	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nov 2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nov 2020	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pfizer considers that TNFi adalimumab, is the most relevant comparator in the current appraisal because it:

- Is a NICE-recommended treatment option for patients with AS who responded inadequately to, or who could not tolerate, conventional therapy (NSAIDs),
- Has the highest market share of all bDMARDs in axSpA in terms of volume to the NHS (Table 1; [redacted] in November 2020) and is similarly prescribed for nr-axSpA as it is for AS according to one clinical expert,
- Showed similar overall health benefits with other TNFis in a NICE MTA (TA383) of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. The NMA from NICE TA407 of secukinumab corroborated both these findings and showed that secukinumab provides similar benefits to TNFis, including adalimumab (1, 4). In TA718 the committee considered that TNFis and IL-17s would be similar in terms of effectiveness.
    - The Assessment Group for TA383 assumed a class effect of TNFis (that is, the quality adjusted life years (QALYs) gained are the same for each) based on their review of the clinical evidence. Therefore, the difference in ICERs between each TNFi was driven entirely by different acquisition and administration costs (1).
- Adalimumab is likely to have the cheapest net price, as biosimilar versions are available in the UK.

Table 2 summarises the Decision Problem for this submission. Further details of the clinical pathway of care are described in Section The Ankylosing Spondylitis QoL (ASQoL) is a disease-specific QoL instrument developed from interviews with AS patients. The items most often reported by patients were related to pain, mood, sleep disturbance, and decreased functioning, especially related to household tasks, family activities, dressing and personal hygiene (31, 40).

B.1.3.3 Clinical pathway of care.

Table 2: Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs	People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs	Not applicable
Intervention	Tofacitinib	Tofacitinib	Not applicable
Comparator(s)	Interleukin-17A inhibitors: • Secukinumab • Ixekizumab TNFis including: • Adalimumab • Certolizumab pegol	TNFi adalimumab	• Adalimumab is the most prescribed Biologic disease-modifying anti-rheumatic drug (bDMARD) in AS (Table 1). • Adalimumab has demonstrated similar health benefits to other TNFis and IL-17s. The NICE Assessment Group for TA383 assumed a class effect for TNF-alpha inhibitors. In TA407 and TA718, the committee concluded that all treatments results in similar QALYs. • Adalimumab is likely to have the cheapest net price, as biosimilar versions are available in the UK.

	• Etanercept • Golimumab • Infliximab		
Outcomes	• Disease activity for example, Assessment of SpondyloArthritis International Society (ASAS) • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, periph	Disease activity outcomes (ASAS20, ASAS40, ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score- C-reactive protein), Biologic disease-modifying anti-rheumatic drug (BASDAI), Bath AS Metrology Index (BASMI)) Functional capacity (BASFI) Disease progression (change in BASFI) Pain (Total back pain, Nocturnal Spinal Pain) Peripheral symptoms (Maastricht Ankylosing Spondylitis Enthesitis Score (MASES))	Outcomes addressed in this submission include the key clinical outcomes reported in TA383, TA407 and TA718, and those used in the respective cost effectiveness analyses. Symptoms of extra-articular manifestations are not reported in this submission as neither trial was sufficiently powered to detect differences between arms. Pfizer has compared tofacitinib with adalimumab in the network meta-analysis (NMA) in disease progression and function using the following outcomes: • BASDAI change from baseline score; • ASAS20, ASAS40 and ASAS5/6 (the later three combining disease activity and disease function measures, including the BASFI)

	eral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • Adverse effects of treatment • Health-related quality of life (HRQoL)	HRQoL outcomes (AS quality of life (ASQoL), SF-36v2, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)) Safety outcomes • overall discontinuations • Adverse event (AE)-related discontinuations • Serious infections	
Economic analysis	The reference case stipulates that the cost	A [redacted] was carried out.	Tofacitinib provides [redacted]. The [redacted].

	effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case	Costs are considered from an NHS and Personal Social Services perspective. The patient access scheme for tofacitinib has been included as part of the analysis. The [redacted] model considered the costs of biosimilars.	

	stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent		

	treatment technologies will be taken into account.		
Subgroups to be considered	None	None	Not applicable
Special considerations including issues related to equity or equality	None	None	Not applicable

B.1.2 Description of the technology being appraised

Table 3 provides an overview of tofacitinib. The draft Summary of Product Characteristics (SmPC) is included in **Appendix C**; however, at the time of submission, a European public assessment report (EPAR) is not available.

Table 3: Description of the technology under appraisal

Name and brand name	Tofacitinib (Xeljanz)
Mechanism of action	Tofacitinib (Xeljanz) is a potent Janus kinase-1 (JAK-1) and JAK-3 inhibitor and is a targeted synthetic small molecule. It interrupts the signal transduction of cytokines that contribute to the aberrant immune response in AS (7, 8). Janus kinases (JAK) are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of creating new blood cells in the body (haematopoiesis) and immune cell function. Activation of JAK pathways initiates the expression of survival factors, cytokines, chemokines and other molecules that facilitate leucocyte cellular trafficking and cell proliferation, contributing to inflammatory and autoimmune disorders. There are currently no JAK inhibitors recommended for the treatment of adult AS by NICE.
Marketing authorisation/CE mark status	Tofacitinib does not currently have marketing authorisation (MA) for the indication in this submission. An application for this MA was submitted to the European Medicines Agency (EMA) in February 2021. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) has been published on 14 October 2021 and MA from the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] for this indication. Tofacitinib already has marketing authorisation in the UK for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis in adults and in juvenile idiopathic arthritis in children.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. Other indications for which tofacitinib is licensed in the UK, are: *Rheumatoid arthritis* Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Tofacitinib can be given as monotherapy in cases of intolerance to MTX or when treatment with MTX is inappropriate.

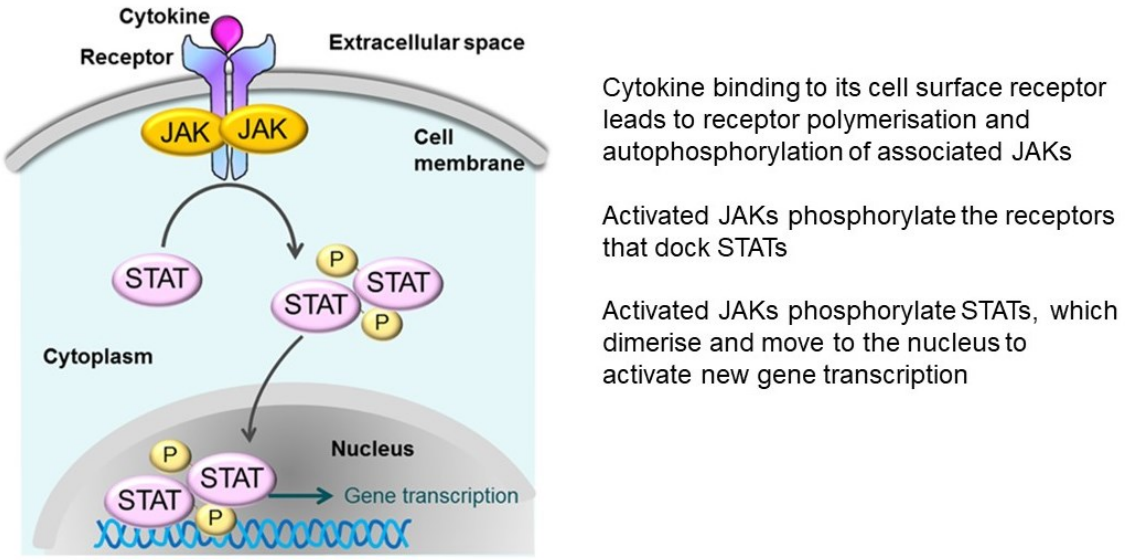
	Psoriatic arthritis Tofacitinib in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. *Ulcerative colitis* Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. *Juvenile idiopathic arthritis (JIA)* Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+]or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
Method of administration and dosage	The recommended dose is a 5 mg tablet administered twice daily (BID). Tofacitinib is given orally with or without food. For patients who have difficulties swallowing, tofacitinib tablets may be crushed and taken with water.
Additional tests or investigations	The introduction of tofacitinib would not require additional tests, investigations or administration beyond those that are currently required for all patients with AS, other than the assessment of lipid parameters taken once, at week 8, following the initiation of treatment. Furthermore, tofacitinib would not require additional monitoring of patients with AS compared to other indications.
List price and average cost of a course of treatment	The list price of a 56-tablet pack of 5 mg tofacitinib is £690.03 (excluding VAT; British National Formulary (BNF) online [2021]). The cost per patient estimated at £8,995 for the first and subsequent 12 months based on the list price.
Patient access scheme/commercial arrangement (if applicable)	The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of tofacitinib, with the discount applied at the point of purchase or invoice. The current patient access scheme for tofacitinib will also apply to the AS indication. [redacted]

Abbreviations: AS: ankylosing spondylitis; BID: Twice daily; BNF: British National Formulary; CV: Cardiovascular; CHMP: Committee for Medicinal Products for Human Use; DMARD: Disease-modifying anti-rheumatic drug; EMA: European Medicines Agency; FDA: Food and Drug Administration; JAK: Janus kinase; MA: Marketing authorisation; MACE: Major adverse cardiovascular events; MHRA: Medicines and Healthcare products Regulatory Agency; MTX: Methotrexate; NICE: National Institute of Health and Care Excellence; NMSC: Non-melanoma skin cancer; NSAIDs: Non-steroidal anti-inflammatory drugs; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; SPC: Summary of product characteristics; TB: Tuberculosis; UC: Ulcerative colitis

B.1.2.1 Tofacitinib's mode of action

The pathogenesis of AS is driven by pro-inflammatory cytokines and chemokines activating immune cells. Many of these cytokines utilise the JAK-signal transducer and activator of transcription (STAT) pathway to induce the intracellular signalling cascade that leads to the inflammatory response. JAKs are non-receptor protein tyrosine kinases that associate with cytokine receptors. There are four members of the JAK family: JAK1, JAK2, JAK 3 and TYK2; each JAK has specificity for a different set of cytokine receptors and each cytokine receptor needs at least two associated JAKs in order to signal (9). Consequently, different combinations of JAKs are associated with different cytokine receptors. Binding of the cytokine to its receptor activates JAK, which then phosphorylates the cytokine receptor to allow binding of STATs. The STATs are phosphorylated by JAK and released into the cytoplasm, where they form dimers and translocate to the cell nucleus. Here, STATs activate gene expression, leading to further cytokine production and therefore further immune cell activation (9, 10) (Figure 1).

Figure 1: The JAK-STAT signalling pathway



Abbreviations: JAK: Janus kinase; P: phosphate group; STAT: signal transducer and activation of transcription

Tofacitinib preferentially inhibits signalling by cytokine receptors that associate with JAK3 and/or JAK1 (9). The pairing of JAK3 with JAK1 is associated with cytokines that signal through the gamma common chain-containing receptor, including IL-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation,

and function. Other pairs containing JAK1 are associated with additional pro-inflammatory cytokines, including IL-6 and interferon-ɣ.

By targeting the JAK/STAT pathway, tofacitinib can modulate the response to multiple cytokines, which results in modulation of the immune and inflammatory response underlying the complex pathogenesis of AS.

B.1.3 Health condition and position of the technology in the treatment pathway

- AS is a common disease in young adults, with a peak age of onset in their 20s to 30s (11).
- People with axSpA (including those with AS) are more likely to remain single or divorce than the general population and women with axSpA are less likely to have children (12).
- An estimated 10 – 40% of people with axSpA (including those with AS) have to give up work and tend to retire 9.5 years earlier than the general population. 3.5% of people with axSpA report absenteeism at work (12).
- Extra-articular manifestations such as uveitis (prevalence of 22–37%); inflammatory bowel disease (IBD) (4-16%); psoriasis (4–9%) are common in AS (13-18).
- Comorbidities such as arthritis (18%-58%) are common in AS (13-18).
- Current treatment options for patients with active AS following treatment with NSAIDs are TNF inhibitor therapy and IL-17 inhibitors (2)
- Between 20-40% of patients with AS do not respond or are intolerant to TNF inhibitor (TNFi) therapy and, among those that do respond, not all achieve remission (8, 19).
- Clinical responses to TNFi declines with each subsequent treatment, evidenced by a higher incidence currently failing their 2nd or 3rd TNFi (20).
- IL-17 inhibitors may also induce or aggravate inflammatory bowel disease (IBD) which is prevalent in an estimated 4-16% of patients with AS and is not recommended for use in patients with IBD (11, 13, 21).
- Patients with rheumatological conditions have been shown to prefer oral therapies over injectables due to ease of administration, however, current AS treatment options are limited to subcutaneous (SC) and intravenous (IV) routes of administration (22).
- Tofacitinib will provide a new mechanism of action as an oral alternative treatment option for people with active AS for whom NSAIDs, have been inadequately effective or not tolerated.

B.1.3.1 Disease overview

Disease description

Ankylosing spondylitis (AS) and nr-axSpA are part of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis (Figure 2), which share common genetic, histological and clinical features (also

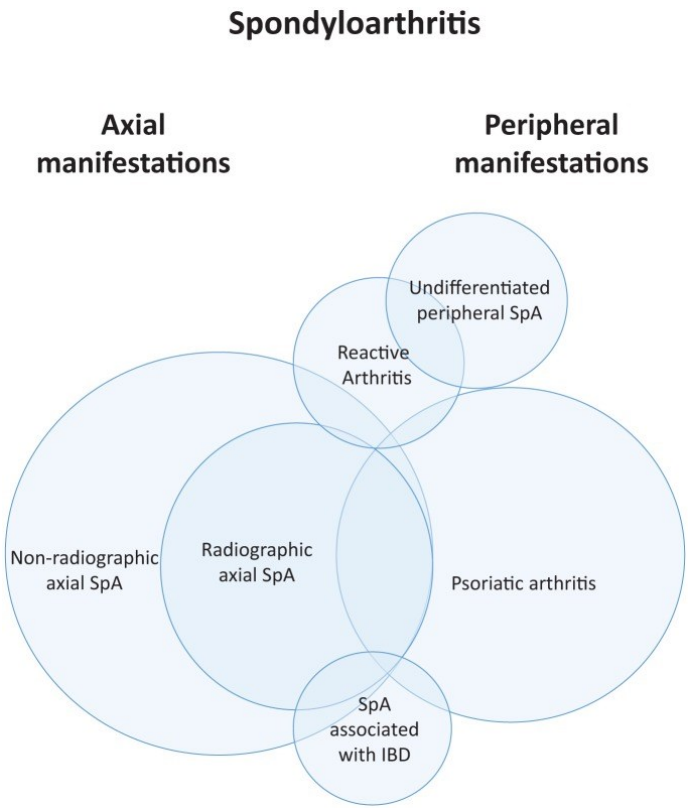
including psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis and undifferentiated spondyloarthritis) (23). Spondyloarthritis can be categorised as having either predominantly axial or peripheral involvement (23). AxSpA can either be radiographic axial spondyloarthritis, also known as AS or nr-axSpA. Peripheral spondyloarthritis includes arthritis (96-98%), dactylitis (40-49%), and enthesitis (41-48%) (24, 25).

In people with axSpA, the predominant symptom is back pain with inflammation of the sacroiliac joints (sacroiliitis [SI]) or the spine, or both (26-28). If x-rays of the sacroiliac joints and spine are normal, but there are other objective signs of inflammation (elevated CRP or evidence on magnetic resonance imaging [MRI]) the disease is classified as nr-axSpA. If inflammation is visible on x-ray as erosions, sclerosis (thickening of the bone), and partial or total ankylosis (fusion of joints), the disease is classified as radiographic axial spondyloarthritis (AS)(26-28).

AS predisposes people to at least a two-fold increased incidence of vertebral fragility fractures (29). These patients are also at increased risk of atlantoaxial subluxation, spinal cord injury, and, rarely, cauda equina syndrome. The onset of symptoms typically occurs in the third decade of life, but it can be 7–10 years before a diagnosis is made. Many patients with mild disease may remain undiagnosed (29). The main symptoms can include back pain, usually inflammatory in nature, arthritis (inflammation of the joints in other parts of the body), enthesitis (inflammation where a bone is joined to a tendon), and fatigue. Involvement of the spine and SI joints, peripheral joints, digits, entheses are characteristic of the disease. Impaired spinal mobility, postural abnormalities, buttock pain, hip pain, peripheral arthritis, enthesitis, and dactylitis are all associated with AS (29).

Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. There may also be peripheral joint involvement or extra-articular manifestations such as uveitis (prevalence of 22–37%); IBD (4-16%); psoriasis (4–9%) are common in AS (13).

Figure 2: The spectrum of spondyloarthritis (SpA) and overlap between different SpA forms



Source: (30)

IBD, Inflammatory Bowel Disease

Epidemiology

AS is a common disease in young adults, with a peak age of onset in their 20s to 30s (11). Due to the early onset of AS, patients have to adjust to their disease for most of their lives (31). The prevalence of AS in a UK general population sample of primary care has previously been estimated to be 13.4 per 10,000. Furthermore, from the same population, approximately one-third of patients were managed within secondary care rheumatology services (32).

B.1.3.2 Disease burden

AS represents a major burden and can affect morbidity, increase mortality, negatively impact QoL and reduce participation in paid and unpaid work (33).

Co-morbidities

In addition to the spinal pain most often associated with AS, people with the condition can also have a range of co-morbidities (12).In AS, previous studies have reported (reported at any time during the disease course) (13):

- 18–58% prevalence of arthritis,
- 34–74% prevalence of enthesitis and
- 6–8 % prevalence of dactylitis.

Extra-articular manifestations

People with AS can also have a range of complications (12):

- The reported prevalence of uveitis occurring at some point in time during the course of the disease (AS) varies from 22–37%; Uveitis is a condition which can cause blindness (12, 13, 34).
- The prevalence of IBD in AS is estimated at 4–16%; IBD can lead to permanent damage and the need for invasive surgery and the use of colostomy bags (12, 13).
- The prevalence of psoriasis in AS was reported to be between 4–9% (12, 13).

Social impact

Patients with AS experiencing symptoms of fatigue have expressed having a lack of enthusiasm and difficulties concentrating when doing social and work tasks (35). There have also been reports of negative impacts on patients with AS including changes in mood or personality, effects on social life and relationships with friends and family, low self-esteem, stigma and worry about the future and poor cognition and memory (35, 36). The invisibility of this condition means it is often difficult to communicate its impact to loved ones, leading to a profound effect on relationships – people with axSpA (including those with AS) are more likely to remain single or divorce than the general population and women with axSpA are less likely to have children. It is rare that any sort of counselling service is offered to someone with axSpA, with just 7.5% of clinics reporting that they offer psychological support as part a multidisciplinary team (12).

Economic and employment impact

In a UK study of 612 AS patients, employment rates were 14% lower than the UK national average, with 40% of patients of working age being unemployed, 44% of whom related this to poor health (33). Another UK study found that the majority of the total cost of AS in the UK per patient per year were work-related costs, due to inefficient working hours, early retirement and unpaid carer's time (37). In addition, unemployment, work disability and loss of productivity at work has been shown to be associated with, social deprivation, longer disease duration, functional impairment and depression (33, 38).

Quality of life

Significant differences in QoL outcomes for physical and psychosocial domains have been observed between AS patients and the general population (31, 39).

- In an international longitudinal, observational study, a greater proportion of patients with AS reported moderate to severe limitations in mobility, selfcare, daily activity, pain, and anxiety (the 5 EuroQoL domains) than reported in the general population (31).
- Diminished social functioning experienced by patients with AS was found to be similar to that seen in patients who have lost a limb (31).
- In a separate study, AS patients with high disease activity and who were refractory to conventional treatment had lower scores in all domains of QoL (Medical Outcome Survey SF-36) when compared with patients with hypertension, diabetes, or arthritis, with scores comparable to patients with chronic heart failure (39).
- The Ankylosing Spondylitis QoL (ASQoL) is a disease-specific QoL instrument developed from interviews with AS patients. The items most often reported by patients were related to pain, mood, sleep disturbance, and decreased functioning, especially related to household tasks, family activities, dressing and personal hygiene (31, 40).

B.1.3.3 Clinical pathway of care

Conventional therapy for AS includes anti-inflammatory treatment with NSAIDs and physiotherapy (Figure 3). NSAIDs are offered at the lowest effective dose to people with pain associated with AS. Appropriate clinical assessments are also considered

for patients with AS, risk factors are monitored on an ongoing basis and gastroprotective treatment may be initiated. If an NSAID is given at the maximum tolerated dose for 2–4 weeks and does not provide adequate pain relief, the NSAID could be switched to another (2).

TNFis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy. NICE technology appraisal TA383 recommends adalimumab, certolizumab pegol, etanercept, golimumab and infliximab as treatment options for adults with severe active AS in adults whose disease has responded inadequately to, or who cannot tolerate NSAIDs (1) (Figure 3). Biosimilar versions of adalimumab, etanercept and infliximab are available, though infliximab is only recommended if the least expensive infliximab product is used (1). NICE technology appraisal 407 recommends the IL-17A inhibitor secukinumab as an alternative to, or after inadequate response to TNF-alpha inhibitors (4). Similarly, ixekizumab is also an IL-17A inhibitor and is recommended by NICE for adult patients with active AS for whom NSAIDs and TNFis have been inadequately effective or not tolerated or for whom TNFis are contraindicated (3).

The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available (1). This may include considering associated conditions such as extra-articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen (1).

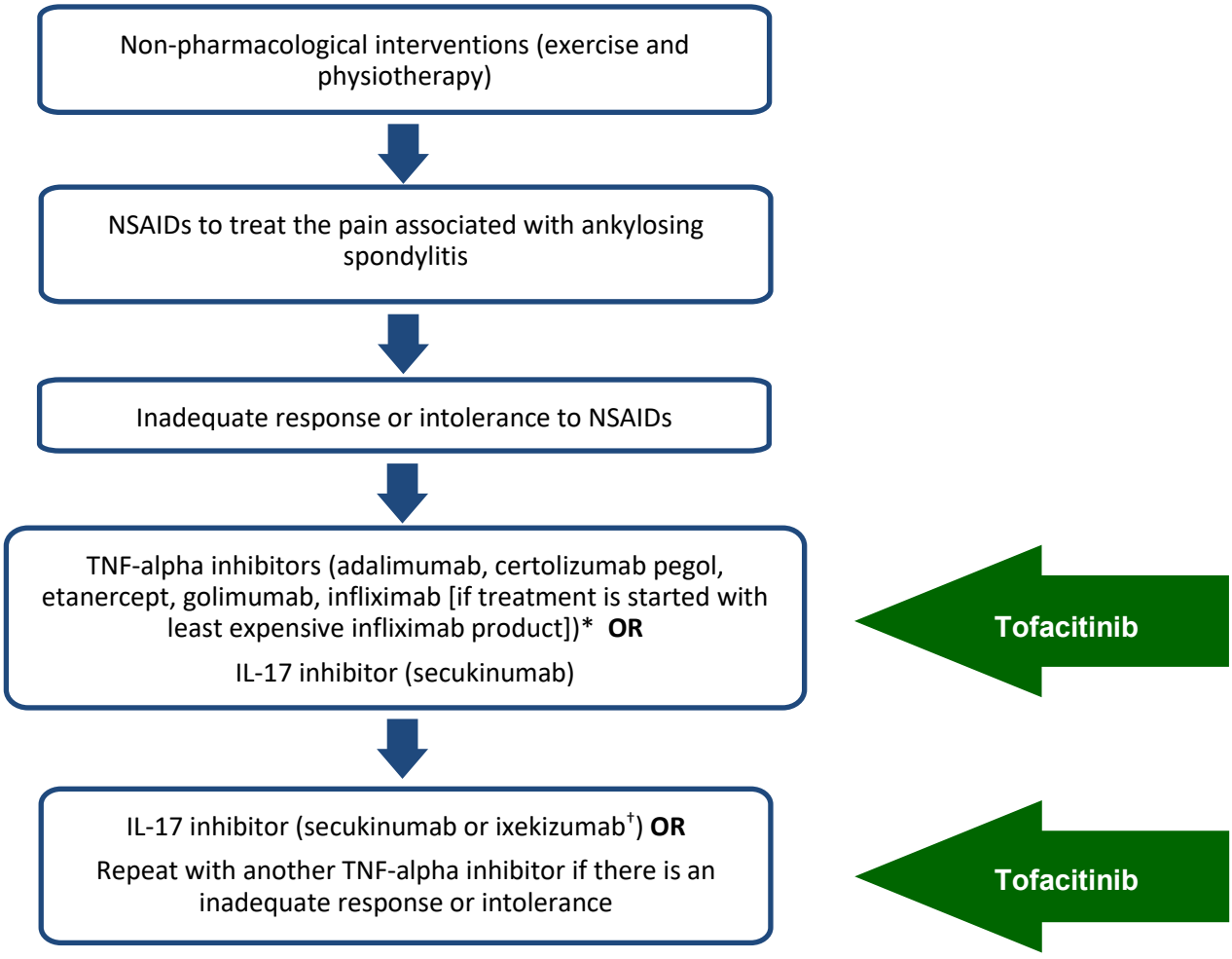
The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment whereas the response to secukinumab should be assessed after 16 weeks of treatment. Treatment should only be continued if there is clear evidence of response, defined as a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more (1, 4). When using BASDAI and spinal pain VAS scores, healthcare professionals should consider any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires and make any adjustments they consider appropriate (1, 4).

Treatment with another TNFi is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNFi, or whose disease has stopped responding after an initial response (1).

B.1.3.4 Proposed place for tofacitinib in the treatment pathway

Figure 3 shows the clinical pathway of care for AS and the proposed position of tofacitinib in the AS treatment pathway. It is anticipated that tofacitinib will be used as an option for treating active AS in adults whose disease has responded inadequately to NSAIDs or TNFis. It will be applicable both to biologic-naïve and biologic-experienced patients (i.e. it could be used immediately after failure of NSAIDs, or after failure of a biologic DMARD).

Figure 3: Clinical pathway of care for ankylosing spondylitis



*The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

†Ixekizumab is recommended only if TNFis are not suitable or do not control the condition well enough.

SOURCE: (2, 3)

B.1.3.5 Clinical need and practice

Current treatment options for patients with active AS following treatment with NSAIDs are TNFis and IL-17 inhibitor therapy (8). Although these are effective in a significant proportion of patients, not all patients respond, and some are intolerant to these treatment options. Between 20-40% of patients with AS do not respond or are intolerant to TNFis and in addition, patients who discontinue TNFi therapy often experience disease relapse upon its reintroduction (8).

A large multinational, real-world study of TNFi use in patients with AS demonstrated that TNFi do not consistently deliver sustained efficacy (20). The study reported that clinical responses to TNFis declined with each subsequent treatment, evidenced by a higher incidence of failure of response to 2nd or 3rd TNFi (20). The study also reported that the most common reasons for switching were secondary (loss of response over time) and primary lack (initial non-response) of efficacy (43.8 and 16.1%, respectively), worsening of condition (35.1%), remission not induced or maintained (20.7 and 15.7%, respectively), lack of alleviation of pain (19.4%) and lack of tolerability (12.0%) (20, 41, 42). In addition, a NICE committee for TA383 noted comments from experts who suggested that there are also differences between the TNFis in their effects on extra-articular manifestations, based on individual patient characteristics (1).

IL-17 monoclonal antibody therapy, secukinumab, has been shown to have a similar treatment effect with TNFis (1, 4). However, secukinumab and other IL-17 inhibitors may induce or aggravate IBD which is prevalent in an estimated 4-16% of patients with AS (11, 13, 21). There are many issues worthy of consideration in clinical drug selection for treating AS and this may limit treatment options (11). There is a clear unmet need for further options in the treatment of AS (43).

Tofacitinib provides an alternative mechanism of action by selectively inhibiting the JAK family of kinases, leading to direct and indirect inhibition of cytokine pathways and a subsequent reduction of inflammation in AS.

Oral versus injectable therapies

Given that bDMARDs are administered parenterally, there is an unmet need for an oral therapy. Patients with other rheumatological conditions have been shown to prefer oral therapies over injectables due to ease of administration (22), however, current AS treatment options are limited to SC and IV. Tofacitinib will provide an alternative treatment option for people with active AS for whom NSAIDs, have been inadequately

effective or not tolerated. As an oral JAK inhibitor indicated for AS, tofacitinib provides an alternative route of administration that eliminates the physical and psychological patient burden of injections.

B.1.4 Equality considerations

No equality issues have been identified.

B.2 Key drivers of the cost effectiveness of the comparators

Key points

- Key clinical outcomes reported in TA383, TA407, and TA718 were ASAS 20, ASAS 40, BASMI, BASFI, BASDAI and BASDAI50.
- Key clinical outcomes included in the cost-effectiveness models of TA383, TA407 and TA718 were treatment response (BASDAI50) and disease progression (changes from baseline for BASFI and BASDAI), serious infections and tuberculosis reactivation.
- The appraisal committees for previous TAs in AS concluded that TNFi therapy should be considered as a class and are broadly similar given the lack of difference in effect between them (TA383), and that secukinumab has a similar efficacy to TNFis (TA407). In TA718 the committee considered that TNFis and IL-17s are similar in effectiveness (3).
- The difference in the ICERs between the individual TNFis in TA383 and TA407 was driven entirely by different acquisition and administration costs.

Published NICE technology appraisals in AS were reviewed to identify key drivers of cost-effectiveness for the relevant comparators:

- ***TA383:*** TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondylarthritis (1)
- ***TA407:*** Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (4)
- ***TA718:*** Ixekizumab for treating axial spondyloarthritis after NSAIDs (3)

The drivers of cost-effectiveness, along with the main areas of uncertainty are summarised below for each appraisal, categorised as clinical outcomes and measures, outcomes used in the cost effectiveness analysis, drivers of cost effectiveness and resource use assumptions.

B.2.1 Clinical outcomes and measures

TA 383: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondylarthritis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) (1)

Overview of clinical outcomes and measures

Efficacy: The assessment group carried out a network meta-analysis (NMA) looking at both continuous and binary efficacy and QoL outcomes at 10–16 weeks across comparators. Outcomes reported and included in the NMA for the majority of comparators were ASAS20, ASAS40, BASDAI 50, BASFI, BASMI, SF-36v2 and MASES (1).

The NMA compared individual TNFis with each other and TNFis as a class compared with placebo. The results of the meta-analysis showed a consistent beneficial effect across all five TNFis at 10–16 weeks, compared with placebo (individually and as a class) and no statistically significant differences between the five TNF-alpha inhibitors for efficacy outcomes (1).

Adverse events: The Assessment Group evaluated AE rates from a Cochrane Review and NMA of nine biological interventions (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab). Analysis of the Cochrane Review showed that, as a group, TNFis are associated with significantly higher rates of serious infections, tuberculosis reactivation, non-melanoma skin cancer, total adverse events, and withdrawals because of adverse events, when compared with control treatments in the short term. When individual TNFis were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments (1).

Overview of outcomes used in the cost-effectiveness analysis

The Assessment Group developed a de-novo model (hereby referred to as the 'York model') which leveraged a more explicit approach to modelling the long-term impact of TNFis on the progressive nature of the disease. The committee focused on the assessment group's York model for its decision-making purposes (NICE TA383 2016).

This model adopted a simplified decision tree structure with a lifetime time horizon and in common with the manufacturer models, short-term clinical effectiveness was based on outcomes from the available clinical data. Outcomes used in the York model are as follows (1):

Initial response: This was determined based on BASDAI 50 at 12 weeks, in line with the British Society for Rheumatology guidelines (44) and previous NICE appraisals (1, 4). This was considered an appropriate measure of response by the committee. The Committee concluded that the decision to continue treatment in clinical practice should be based a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain VAS by 2 cm or more. The committee also noted that in clinical practice, response can be assessed later than 12 weeks from treatment initiation, up to 6 months post-initiation (1).

Disease progression/ disease state: Disease states were defined by the change from baseline for BASDAI and BASFI scores and progression into these states were defined by changes in these two measures. The York model based the initial change in BASDAI and BASFI on the average mean change reported in BASDAI and BASFI estimated for responders and non-responders. The Assessment Group also used a new approach to model long-term disease progression and the impact of treatment on the natural history of disease, by relating the assumptions more explicitly to the existing clinical data for TNFis. Specifically, the Assessment Group accounted for the independent effects of symptomatic improvements (that is, a reduction in disease activity according to BASDAI) on BASFI scores. It also considered the effect of changes in radiographic progression (measured by mSASSS) on BASFI. Because of these analyses, the model assumed that patients who continued to have, and whose disease responded to ('responders'), a TNFi after Week 12 had a slower progression rate (according to BASFI scores) compared with the natural history of the disease (this effect was delayed until year 4). Despite agreeing that the precise long-term BASFI was uncertain, the committee agreed that it should continue to deteriorate during treatment but at a slower rate compared to the natural history of the disease (1).

The rebound effect after treatment withdrawal (in patients whose disease initially responded but then stopped responding to therapy) was a noted uncertainty in disease progression with two scenarios modelled (1):

- A rebound to baseline for progression of BASDAI and BASFI, where the BASDAI/BASFI of patients failing therapy deteriorate by the same amount it improved while responding to therapy
- A rebound back to natural disease history where BASFI deteriorates to the level it would have been if these patients had not responded to therapy

The committee considered the rebound to baseline as the most plausible option (1).

Efficacy of sequential treatment with TNFis in AS: The committee agreed on the importance of considering treatment with a second or third TNFi and noted that real world evidence (RWE) data suggested a 30% reduction in response rate with each subsequent treatment (10% absolute reduction). It heard from the Assessment Group that this implies that the ICER would be correspondingly higher, but that the Assessment Group had not modelled sequential use (1).

Utility: The committee noted that, although the models from the companies and the Assessment Group all used changes in BASDAI and BASFI scores to model costs and utilities, the underlying assumptions in each model were different. The preferred approach was the approach that was submitted by Pfizer for the etanercept submission. Separate algorithms were used for each population, using data from the 1031 study (45) and the 314-EU study (46) (both mapped to European Quality of Life Five Dimension (EQ-5D)) (1).

Extra-articular manifestations: The Committee was aware that potential differences between the TNFis in their effects on extra-articular manifestations may have cost implications but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness (CE) analysis.

Adverse events: The only adverse event costs included in the model were serious infections and tuberculosis reactivations.

Drivers of CE: As the ERG NMA suggested similar effectiveness among different TNFis, the York model assumed a class effect, where the treatment effect (based on BASDAI50, BASFI and BASDAI change from baseline) for all TNFis are the same, resulting in the same amount of QALYs. With this assumption, the committee concluded that the difference in ICER between different TNFis was mainly driven by their acquisition and administration costs. The final appraisal determination also stated

that ICERs were sensitive to assumptions about the magnitude of the difference in baseline BASDAI/BASFI scores between 'responders' and 'non-responders'. That is, ICER estimates (TNFis vs conventional care) became more favourable towards the TNFis when smaller differences between the baseline scores of 'responders' and 'non-responders' were assumed.

TA407: Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (4)

The MEASURE 1 (47) and MEASURE 2 (48) trials, which compared secukinumab with placebo in active AS, informed the appraisal of secukinumab, and were considered to be generalisable to the UK population (4).

Overview of clinical outcomes and measures

Efficacy: The primary outcome measure in the MEASURE trials was the proportion of patients who had an ASAS 20 response at week 16. The proportion of patients whose BASDAI score improved by 50% from baseline, and also the change in BASFI score from baseline, were collected as secondary endpoints. Other secondary outcomes included the proportion of patients achieving ASAS40 response at week 16, the proportion of patients achieving ASAS 5/6 response criteria at week 16, BASDAI change from baseline at week 16, SF-36v2 PCS change from baseline at week 16, ASQoL change from baseline at week 16, and the proportion of patients achieving ASAS partial remission criteria at week 16 (4).

The committee noted that the MEASURE 1 and 2 trials assessed patients at 16 weeks (in accordance with the marketing authorisation). This is longer than the majority of other studies (such as those of TNFis) in AS which typically report outcomes after 12 weeks. The committee noted, and the clinical experts confirmed, that the magnitude of response in the MEASURE trials was broadly stable between 12 and 16 weeks. The committee concluded that the outcome measures used in the trials were appropriate, and that the 16-week assessment of response was in line with the marketing authorisation, and acceptable for decision making. It was concluded reasonable for the company to include MEASURE1 and 2 in its meta-analysis (4).

Network meta-analysis: The company conducted an NMA to estimate the relative effectiveness of secukinumab 150 mg and relevant comparators (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab). The company conducted the comparison using separate networks for clinically relevant outcomes of ASAS20 response, ASAS40 response, BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline. The base case analysis was based on the timepoint of the primary endpoint for each comparator between weeks 12 and 16 and included both the MEASURE 1 and MEASURE 2 studies of secukinumab (4).

The committee concluded that secukinumab has a similar efficacy to the TNFis (4).

Adverse Events: A secondary outcome in MEASURE 2 and MEASURE 1 was to evaluate the overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring. The committee concluded that the adverse effect profile of secukinumab is acceptable (4).

Overview of outcomes used in the cost effectiveness analysis

The company based their model structure on the York model developed for NICE's technology appraisal guidance on TNFis for AS (NICE TA407 2016), and therefore used the same outcomes and approach as the York model to model treatment response (BASDAI50) and disease progression (change from baseline BASFI and BASDAI) and to map utility (change in BASDAI and BASFI scores). The committee concluded that for the purposes of this appraisal, the broad principles of the York model were appropriate (4).

Adverse events: Similarly to the York model the only adverse events considered in the model were serious infections such as tuberculosis reactivation (4).

Drivers of CE: The final appraisal document for TA407 reports that the main drivers of CE were the cost of secukinumab and the choice of network meta-analysis.

To explore the impact of NMA variables of concern, a scenario was explored by the ERG using the mixed treatment comparison (MTC) results derived using a time to response of 12 weeks instead of 16 weeks and using a standard withdrawal rate for all treatments as in the York model. This analysis did not increase ICER for secukinumab compared with any of its comparators beyond what is usually considered

cost-effective (NICE TA407 2016). The committee concluded that secukinumab could be considered a cost-effective use of NHS resources for the treatment of AS in both TNFi naïve and TNFi experienced patients.

TA718: Ixekizumab for treating axial spondylarthritis after NSAIDs (3)

The main clinical trial evidence came from three international placebo-controlled randomised controlled trials in people who had an inadequate response or intolerance to NSAIDs. Two of the trials were in AS: COAST-V included 341 people who had not had a biologic before, and COAST-W included 316 people who had previously had at least one biologic (a TNFi) (3).

Overview of clinical outcomes and measures

Efficacy: The primary outcome was the proportion of patients who had an ASAS 40 response. Secondary endpoints were the BASDAI 50, and the BASFI score from baseline. Ixekizumab showed a statistically significant clinical effect compared with placebo for all primary and secondary outcome measures (3).

Network meta-analysis: Statistically significant differences were identified for ASAS40, BASDAI50, BASDAI and BASFI score from baseline at Weeks 12–18. For all other comparisons vs ixekizumab, there was no statistically significant difference, or required data were not identified in the clinical SLR (3).

Adverse events: At Week 16 and Week 52, in all treatment arms, most treatment emergent adverse events (TEAEs) reported in COAST-V, -W and -X were mild-to-moderate in severity and serious adverse events (SAEs) occurred infrequently (3).

Overview of outcomes used in the cost-effectiveness analysis

The company presented a Markov model to estimate the cost effectiveness of ixekizumab compared with TNFis, secukinumab (for AS only) and conventional therapy in people for whom NSAIDs or TNFis had been inadequately effective, not tolerated, or contraindicated. The model aligns with the de-novo model ('York model') developed for use in TA383 to evaluate the cost-effectiveness of multiple TNFis in axSpA (see beginning of section B.2.1).

Disease progression/ disease state: The ERG noted that in the economic evaluation, a definition of response based only on BASDAI data are used, while in the clinical practice a broader definition is used. In line with the models used in TA383 and TA407, response criteria were determined by BASDAI50 score, with responders transitioning to 'maintenance treatment' and non-responders to 'conventional care'. BASFI was used to model disease progression over time. The ERG scenario with BASFI rebound to natural history increased the ICER significantly compared to the base case rebound to baseline. Nevertheless, the ERG highlighted that the base-case scenario might be too extreme scenario and that the most plausible situation could be between the two. The company's 'rebound by initial gain' approach reflected the views of the clinical experts that contributed to TA383.

The ERG pointed out that the impact of previous biologic drugs is an area of uncertainty as there is little evidence available; but if the impact would vary between treatments, it was considered that this could have important implications on cost-effectiveness.

Utility: The company's overall approach to estimating utility values is similar to methods used in other previously published axSpA appraisals. The regression model was developed between BASDAI/BASFI data and European Quality of Life Five Dimension Three Level Scale (EQ-5D-3L) utility values cross-walked from European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L) data collected in the trials. The company tested the use of four alternative approaches in scenario analysis. The ERG noted that a large variation in the utilities was produced by using different regression models. The ERG also noted that the range of results calculated by the different regression equations increases with the BASFI score. The ERG noted that the estimates of utility generated by the company's approach are all higher than the estimates generated using the other published regression equations. The ERG has, therefore, presented a scenario analysis in which the Wailoo 2015 (49) regression equation is used to estimate utilities (3). The committees' preferences were to use the most pessimistic method of modelling utility (3).

Adverse events: Similarly to the York model the only adverse events considered in the model were serious infections such as tuberculosis reactivation (3).

Drivers of CE: The appraisal committee in TA718 did not consider that a class effect between TNFis and IL-17s should be assumed, however it concluded that they provide similar QALY gains and therefore similar in terms of clinical effectiveness.

The appraisal committee in TA718 considered that ixekizumab would be used when TNFis are contraindicated or otherwise not suitable, after primary non-response to a TNFi or after a poor response or loss of response to TNFi therapy. It did not consider that a class effect between TNFis and IL-17s should be assumed, however it concluded that they would provide similar QALY gains and therefore can be considered similar in terms of clinical effectiveness (3).

The ERG noted that the company's base-case NMAs were too sparsely populated to generate results for all relevant comparator treatments, so the cost-effectiveness results were informed by the sensitivity NMAs. The ERG was concerned about the substantial differences in the absolute effect estimates generated by the base-case and sensitivity NMAs. The committee agreed with the ERG that the results of the NMAs were not robust and were therefore not suitable for decision making.

The company was requested to analyse the CE of ixekizumab compared with conventional therapy using direct evidence from the COAST trials. The ICERs for ixekizumab compared with conventional therapy using direct data from the COAST trials for people with AS after the failure of TNFis were £18,775 per QALY gained for people who had not had a biologic before and £19,012 for those who had. Therefore, the committee concluded that ixekizumab could be recommended as an option for treating AS and in adults when TNFis have not controlled the condition well enough, or these are not suitable.

A summary of the key clinical outcomes and measures appraised in published NICE guidance can be found in Table 4.

Table 4: Key clinical outcomes and measures appraised in published NICE guidance for the comparator(s)

	Outcome	Measurement scale	Justification	Used in CE model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
NICE TA383	Treatment response	ASAS 20	Primary outcome in clinical trials	Not used in York model	NA: Difference in ICER between different TNFis was mainly driven by their acquisition and administration costs In the Assessment Group's model reduced difference in baseline BASDAI/ BASFI scores between 'responders' and 'non-responders made the ICER estimates more favourable towards the TNFis vs conventional care	BASDAI 50 preferred as a measurement of treatment response	Definition of response in RCT and clinical practice can differ, as can the time of assessment
		ASAS 40	Generally used to measure outcomes in clinical studies	Not used in York model			
		BASDAI 50	Generally used to measure outcomes in clinical studies	Yes			
	Spinal mobility	BASMI	Key measure in clinical trials for spinal mobility	Not used in York model		NA	Results may not reflect clinical practice because some people continued treatment even though their disease did not respond to therapy
	Disease activity	BASDAI (cfb)	In line with previously published models	Yes, BASDI and BASFI were used for: disease state and progression Utility (mapped to EQ5D to derive utilities for model health states)		The committee agreed that the precise long-term BASFI was uncertain. It agreed that it should continue to deteriorate during treatment but at a slower rate compared to the natural history of the disease	
	Functional ability	BASFI (cfb)	In line with previously published models				
NICE TA407	Treatment response	ASAS 20	Primary outcome of the MEASURE-1 and MEASURE-2 trials	No	NA: Main drivers of CE were the cost of secukinumab and the choice of network meta-analysis	While noting the ERG's comment that a patient-level simulation, would have better reflected patient heterogeneity, the dependence between baseline BASDAI and BASFI values, and the change from baseline values and response rates at the end of the	
		ASAS 40	Generally used to measure outcomes in clinical studies	No			
		BASDAI 50		Yes			
	Spinal mobility	BASMI		No			
	Disease activity	BASDAI (cfb)		Yes as with the York			

	Outcome	Measurement scale	Justification	Used in CE model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
	Functional ability	BASFI (cfb)		model to map disease state and progression and utility		induction period, the committee concluded that the broad principles of the York model were appropriate.	
	Quality of life	Utility mapping model derived from MEASURE 1 and MEASURE 2	In line with NICE reference case			No comment by the ERG or appraisal committee recorded	Details of the mapping model not shared by the company
NICE TA718	Treatment response	ASAS 20	Primary outcome in clinical trials	No	-		The method used in the model (only using BASDAI data) to categorise patients as responders or non-responders to treatment does not reflect clinical guidelines
		ASAS 40	Generally used to measure outcomes in clinical studies	No	-		
		BASDAI 50	Generally used to measure outcomes in clinical studies	Yes			
	Spinal mobility	BASMI	Generally used to measure outcomes in clinical studies	No	-	-	-
	Disease activity	BASDAI (cfb)		Yes	The committee considers that the some of the results from the sensitivity NMAs for the rad-axSpA populations (BASDAI score cfb and BASFI score cfb for the biologic-naïve,and BASDAI score cfb for the biologic-experienced) are not suitable for decision making. As these values are used in the company model for the rad-axSpA populations, the cost effectiveness results generated by the company model for the rad-axSpA populations are also not suitable for decision making.		
	Functional ability	BASFI (cfb)		Yes	Change from baseline in ICER with ERG scenario (Biologic experienced AS: changes the ICER with -£4,160,121 (vs conventional care) and +£4,750 (vs adalimumab).	BASFI rebound to natural history upon treatment discontinuation	The ERG considers that the rebound to natural history assumption implies there is no benefit beyond the end of treatment (likely worst case) and the rebound by initial gain assumption implies that all of the initial gain from treatment is maintained beyond treatment discontinuation (likely over-

	Outcome	Measurement scale	Justification	Used in CE model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
							estimating the gains of treatment).
	Quality of life	Regression equations were used to generate utility values from HRQoL data collected in the COAST trials using EQ-5D-5L questionnaires. Utility values were estimated using six different regression equations, all included BASDAI and BASFI scores as parameters.		Yes	Estimates of utility generated by the company's approach are all higher than the estimates generated using the other published regression equations.	Use of an alternative (generally the most pessimistic) method of modelling utility	The relationship between BASDAI, BASFI and HRQoL is uncertain and complicated which casts doubt on the reliability of the utility values used in the company models

Abbreviations: ASAS20: 20% improvement in the Assessment in Ankylosing Spondylitis; ASAS40: 40% improvement in the Assessment in Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50: 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosis Spondylitis Functional Index; BASMI: The Bath Ankylosing Spondylitis Metrology Index; cfb: change from baseline; BSR: British Society of Rheumatology; CE: Cost-effectiveness; EQ-5D: EuroQol- 5 Dimension; ERG: Evidence Review Group; ICER: Incremental cost-effectiveness ratio; MTA: Multiple Technology Appraisal; NA: Not available; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; TNF: Tumor necrosis factor.
Sources: (1); (4); (3)

B.2.2 Resource use assumptions

TA 383: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondylarthritis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) (1)

While the costs in the submission included drug acquisition, administration, initiation and (long-term) monitoring cost and serious adverse events (infections and tuberculosis reactivation), the difference in the ICERs between the individual comparators was primarily driven by acquisition and administration costs due to equivalent class-effect among the TNFis (see also class effect assumption above).

TA407: Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (4)

The company noted that, as with the other licensed biologics for AS, the main resource use with secukinumab is associated with treatment acquisition, administration, and monitoring. Non-drug costs are in line with other subcutaneously administered comparators: initial training on self-injection for most patients and monitoring costs are similar across comparators.

The unit cost inputs into the cost effectiveness model were based on those used in the York model, updated where appropriate to the latest NHS reference costs. The committee concluded that for the purposes of this appraisal, the broad principles of the York model were appropriate. These included:

- Drug acquisition costs (including patient access schemes) and administration costs.
- Health state costs: Disease management costs estimated based on an exponential BASFI regression model, as per York model.
- Costs for adverse events including TB reactivation (weighted average cost of relevant Healthcare Resource Group (HRG) codes for pulmonary, pleural or other tuberculosis events) and other serious infections (these represented the cost of a single event and hence were incurred each time the adverse event occurred within the model).

Acquisition, administration and monitoring costs and resource usage from TA407 (which are based on TA383) are presented in Table 5 and Table 6 below.

Tuberculosis infection unit cost was calculated as £2,570.71 and other serious infection unit cost was £1,299.38.

Table 5: Unit costs and resource use associated with drug acquisition and administration from TA407 (based on and updated from TA383)

Items	Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50mgQW	Adalimumab 40mg	Infliximab 40 mg	Golimumab 50 mg	Reference
Frequency of resource use							
Acquisition cost	List price: £1,218.78 per pack of two 150 mg pre-filled syringes/ SensoReady® pens patient access schemes (PAS) price: not published.	£357.50 per 200 mg pre-filled syringe The NICE MTA in AS also indicates that there is an agreed PAS with the department of health for certolizumab pegol, such that the first 12 weeks of treatment are provided free. This PAS is taken into account in the CEA.	£178.75 per 50 mg pre-filled syringe	£352.14 per 40 mg pre-filled syringe	Originator infliximab: Remicade®: £419.62 per 100 mg vial Average cost per dose calculated as £1,850.59–" Biosimilar infliximab: Remsima: £377.66 per 100 mg vial Inflectra: £377.66 per 100 mg vial. Average cost per dose calculated as £1,665.54	£762.97 per pre-filled syringe. Although the 100 mg pre-filled syringe of golimumab has a higher list price than that of golimumab 50 mg, a PAS has been agreed with the department of health that provides the 100 mg dose of golimumab at the same price as the 50 mg dose.	BNF2015
Administration cost (s.c. therapies –first administration only)	£43.00	£43.00	£43.00	£43.00	NA	£43.00	Assumed self-administered following 1 hour of nurse training on first administration, Personal Social Services Research Unit (PSSRU) 2015
Administration (IV therapy [infliximab] – per administration)	NA	NA	NA	NA	£326.46	NA	NHS Reference Costs 2014-15 (HRG code SB15Z)
No. of doses (month 1-3) –induction period	7.00	9.78	13.00	6.52	3.00	3.00	BNF2015
No. of doses (month 4 -6) –maintenance period	3.00	6.52	13.00	6.52	2.00	3.00	BNF2015
No. of doses (three-monthly period from month 7+) – maintenance period	3.00	6.00	13.04	6.52	1.63	3.00	BNF2015

Abbreviations: AS: ankylosing spondylitis; BNF: British National Formulary; CEA: Cost-effectiveness analysis; HRG: Healthcare Resource Group; IV: intravenous; MTA: multiple technology appraisal; NA: not applicable; NICE: National Institute of Health and Care Excellence; PSSRU: Personal Social Services Research Unit; QW, once weekly; SC: subcutaneous.

Table 6: Unit costs and resource use associated with monitoring from TA407 (based on and updated from TA383)

Cost parameter	Unit costs		Frequency of resource use (all interventions)		
	Unit cost	Reference	First 3 months	Subsequent 3 month periods	Reference
Medical visits					
GP visits	£44.00	Cost of an 11-minute GP appointment, with qualifications, PSSRU 2015	0	0	York model for MTA in AS
Specialist visits	£137.23	NHS Reference Costs 2014-15 HRG code WF01A	2	0.5	York model for MTA in AS
Laboratory tests					
Full blood counts	£2.99	Costs sourced from the York model for psoriatic arthritis (TA199) and updated to 2015 prices using the HCHS inflation index from PSSRU 2015	2	1	York model for MTA in AS
Erythrocyte sedimentation rate	£2.96		2	1	York model for MTA in AS
Liver function test	£0.75		2	1	York model for MTA in AS
Urea and electrolytes test	£1.39		2	1	York model for MTA in AS
Chest radiograph	£26.23		1	0	York model for MTA in AS
Tuberculosis Heaf test	£8.74		1	0	York model for MTA in AS
Antinuclear antibodies	£4.66		1	0	York model for MTA in AS
DNA double-strand test	£4.66		1	0	York model for MTA in AS

Abbreviations: BSR: British Society for Rheumatology; DNA: deoxyribonucleic acid; GP: general practitioner; HCHS: Hospital and community health services; HRG: Healthcare Resource Group; PSSRU: Personal Social Services Research Unit

TA718: Ixekizumab for treating axial spondylarthritis after NSAIDs

Five categories of costs were included in the company model: drug acquisition costs, administration costs, trial period and maintenance health state monitoring costs, health state costs and AEs (3).

Drug acquisition costs were calculated based on the total number of doses for the trial period, number of doses yearly for the maintenance period and the unit cost (cost per dose (3).

Administration unit costs were sourced from PSSRU and NHS reference costs, see Table 7 (3).

Table 7: Administration unit costs used in TA718

Administration method	Cost(£)	Source
Subcutaneous injection	42.00	Nurse (GP practice, cost per hour including qualifications), Unit Costs of Health and Social Care 2018, PSSRU
Intravenous injection	289.00	National Schedule of NHS Reference Costs 2017–18, Chemotherapy (CHEM), Outpatient, SB15Z, Deliver Subsequent Elements of a Chemotherapy Cycle

Abbreviations: CHEM: Chemtherapy; GP: general practitioner; PSSRU: Personal Social Services Research Unit

Monitoring resource use in TA718 is based on TA383 as well (see Table 8**Table 6).** Monitoring costs are sourced from NHS Reference costs and Rodgers et al 2011. Being the latest submission available, sources for the current tofacitinib FTA are the same as used in TA718, but have been updated as per the latest NHS reference costs (see Table 31) (3).

Table 8: Monitoring costs and resource use in TA718

Cost parameter	Trial period (first 3 months)	Maintenance (yearly)	Unit cost	Source
Medical visits				
Specialist visit	2	2	£137.00	NHS Reference Costs 2017–18, code WF01A, Rheumatology
Laboratory tests				
FBC	2	4	£2.51	DAPS05, National Schedule of Reference Costs 2017–18
LFT	2	4	£1.11	DAPS04, National Schedule of Reference Costs 2017–18
ESR	2	4	£2.51	DAPS05, National Schedule of Reference Costs 2017–18
U&E	2	4	£1.11	DAPS04, National Schedule of Reference Costs 2017–18
Chest radiograph (X-ray)	1	0	£31.00	DAPF, National Schedule of Reference Costs 2017–18

Cost parameter	Trial period (first 3 months)	Maintenance (yearly)	Unit cost	Source
THT	1	0	£8.91	Rodgers et al.(2011)
Antinuclear antibodies	1	0	£2.51	DAPS05, National Schedule of Reference Costs 2017–18
DNA double-strand test	1	0	£2.51	DAPS05, National Schedule of Reference Costs 2017–18

Abbreviations: DNA: Deoxyribonucleic acid; ESR: Erythrocyte sedimentation rate; FBC: Full Blood Count; LFT: Liver function test; THT: Tuberculosis test; U&E: Urea and electrolytes.

In alignment with the York model and the model used in TA407, health state costs were modelled as disease management costs, estimated based on an exponential BASFI regression model (3).

Similarly to TA383 and TA407, costs of tuberculosis reactivation (£3,869.10) and severe infections (£3,060.65) were included in the model (3).

B.3 Clinical effectiveness

- Efficacy of tofacitinib 5 mg BID in treating the signs and symptoms of active AS in adult patients who have had an inadequate response to previous NSAID or TNFi treatment has been demonstrated in two randomised, double-blind, placebo-controlled studies (A3921119 and A3921120).
- As evidenced by both studies:
    - **Tofacitinib demonstrated AS-related signs and symptoms alleviation** by showing significantly greater ASAS20, ASAS40 and BASDAI50 response rates compared with placebo at Week 12 (in A3921119 trial) and Week 16 (in A3921120 trial)
        - A high level of **symptom alleviation was consistent across bDMARD-naïve and TNFi-IR patients**
    - Tofacitinib was significantly more efficacious in **improvement of functional capacity** (based on BASFI score) as compared with placebo at Week 12 and Week 16
    - Treatment with tofacitinib significantly improved **impact of AS symptoms on patient's Quality of Life** evidenced by ASQoL. It also significantly **improved the SF-36v2 physical component scores** and FACIT-F measure vs placebo at Week 12 and Week 16
- In the A3921119 study, treatment with tofacitinib led to **greater achievement of MIC improvements in Spondyloarthritis Research Consortium of Canada (SPARCC) spine and SI joint scores** compared with placebo
- As evidenced by the A3921120 study:
    - Tofacitinib has shown **rapid efficacy onset**, confirmed by a significant reduction in disease activity compared with placebo and significant alleviation of back pain in as early as two weeks
    - Tofacitinib-treated patients experienced a **significant reduction in spinal pain as well as improvement in nocturnal back pain** at week 16
    - Tofacitinib-treated patients achieved significantly higher **improvements in disease activity** compared patients treated with placebo as measured by ASDAS-CRP baseline decrease ≥ 2.0 at week 16
    - **Tofacitinib lowered inflammation** by almost 12-fold as measured by reduced hsCRP levels at week 16 compared with placebo

- **Efficacy of tofacitinib was maintained longer-term** as demonstrated by 48-week follow-up data from A3921120 study
- **Tofacitinib was efficacious consistently across subgroups of prior treatment history** (bDMARD naïve and TNFi-IR or bDMARD use [Non-IR]), as assessed by ASAS20 and ASAS40 response rate vs placebo
- **Comparative efficacy:** As no head-to-head clinical trial was conducted to compare tofacitinib with adalimumab, an NMA was conducted. The results show that in tofacitinib, outcomes for ASAS20, ASAS40, BASDAI50, BASDAI, BASFI, and BASMI [redacted].

B.3.1 Identification and selection of relevant studies

To inform the clinical effectiveness section, a systematic literature review (SLR) was designed and conducted to identify trials relevant for the NMA. Studies investigating tofacitinib 5 mg BID that met the inclusion criteria of SLR are described in the following sections. See **Appendix D** for full details of the process and methods used to identify and select the clinical evidence (PICOS criteria, search strategy and strings, full list of included and excluded studies, methodologies and outcomes for each included study, and an assessment of bias across studies).

The proposed population for this technology submission is aligned with the marketing authorisation and will focus on the treatment of adult patients with active AS who have responded inadequately to conventional therapy.

B.3.2 List of relevant clinical effectiveness evidence

The efficacy and safety of tofacitinib has been evaluated in two randomised, double-blind, placebo-controlled studies that provide data for more than 470 patients with AS with active disease who have an inadequate response or intolerance to NSAID therapy:

- A3921119 (NCT01786668): A phase II, randomised, double-blind, placebo-controlled, dose-ranging study of efficacy and safety of tofacitinib in patients with active AS (50)
- A3921120 (NCT03502616): A phase III, randomised, double-blind, placebo-controlled, study of the efficacy and safety of tofacitinib in patients with active AS (51)

There are no trials that directly compare tofacitinib with other active treatments for AS. A summary of both trials is presented in **Table 9** with further details provided in Section B3.3.

Table 9. PICOS Summary of the A3921119 and A3921120 tofacitinib trials

Study	**A3921119 (NCT01786668)**	**A3921120 (NCT03502616)**
Study design	A Phase 2, 16-week (12-weeks of treatment and 4-week washout period), multicenter, randomised, double-blind, placebo-controlled, dose-ranging, parallel group study	Phase 3, multicenter, randomised, double-blind, placebo-controlled efficacy and safety study with a 16-week double-blind phase and a 32-week open-label extension
Population	Patients with AS (defined as Modified New York Criteria for Ankylosing Spondylitis 1984, BASDAI score of ≥ 4 and back pain score BASDAI Question 2 of ≥4 at both screening and baseline) that have active disease despite NSAID therapy or who are intolerant to NSAIDs.	
Intervention(s)	Tofacitinib 2 mg Tofacitinib 5 mg Tofacitinib 10 mg (oral administration twice per day)	Tofacitinib 5 mg (oral administration twice per day)
Comparator(s)	Placebo	Placebo[a]
Indicate if trial supports application for marketing authorisation	yes	yes

Study	A3921119 (NCT01786668)	A3921120 (NCT03502616)
Outcomes reported specified in the decision problem [b]	• Disease activity outcomes (ASAS, ASDAS-CRP, BASDAI, BASMI) • Functional capacity outcomes (BASFI) • Pain (Total back pain, Nocturnal Spinal Pain) • Peripheral symptoms (MASES) • Symptoms of extra-articular manifestations • HRQoL outcomes (ASQoL, SF-36v2, FACIT-F) • Safety outcomes o overall discontinuations[c] o AE-related discontinuations[c] o serious infections	
Other outcomes[b]	• Mean Spinal Mobility • SPARCC score • ASspiMRI • EQ-5D-3L	• Spinal Mobility • WPAI • EQ-5D-L • EQ-VAS • Patient's Global Assessment of Disease (PGA)

Source: (50, 51)

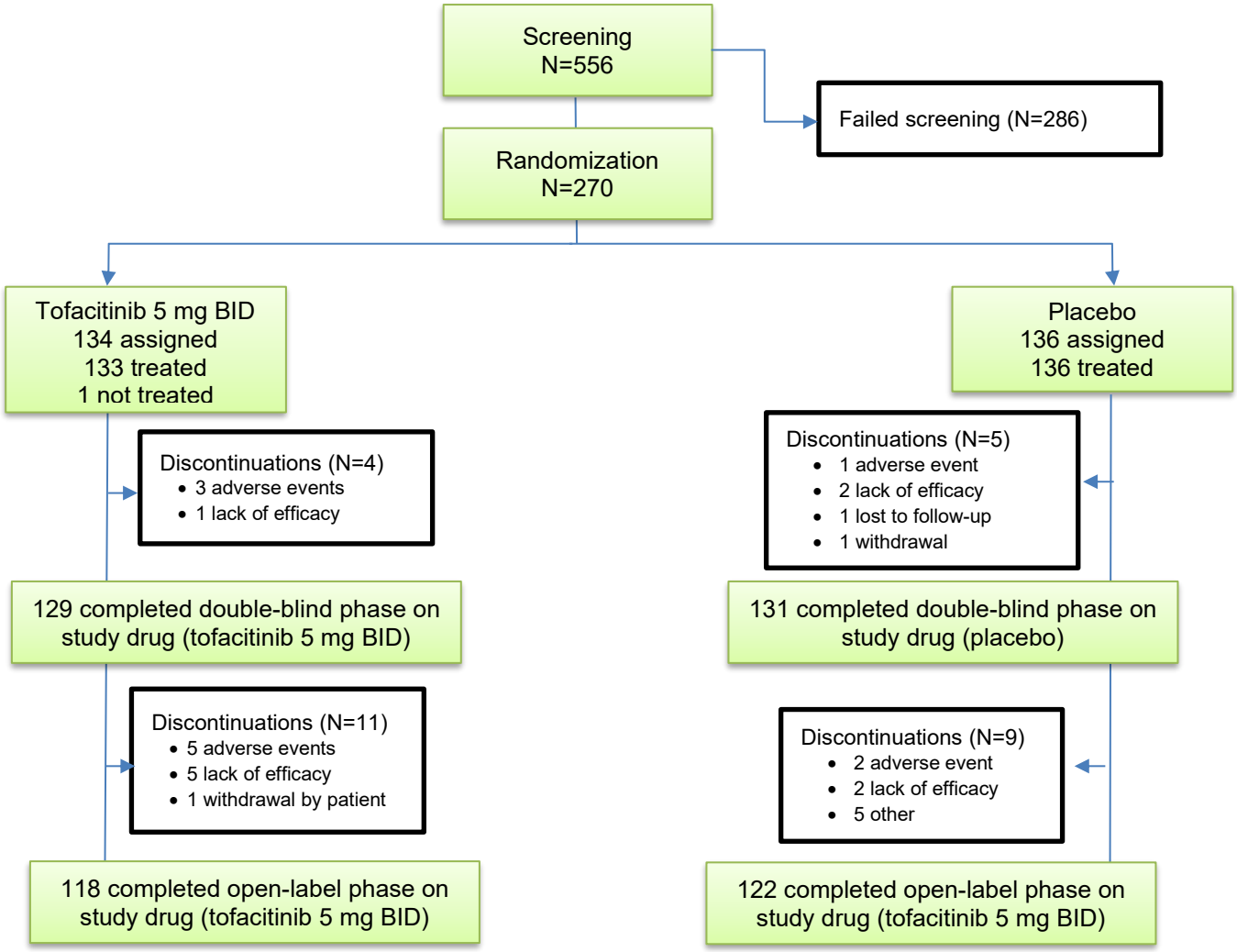
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI, Work Productivity and Activity Impairment; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score Using C-Reactive Protein; EQ-VAS, EuroQol Visual Analogue Scale; AEs, adverse events; ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; EQ-5D, EuroQol 5-dimensions questionnaire; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID, non-steroidal anti-inflammatory drugs; SF-36v2, 36-Item Short Form Survey version 2; SPARCC, Spondyloarthritis Research Consortium of Canada, ASspiMR. Modified Berlin Ankylosing Spondylitis Spine Magnetic Resonance Imaging Activity Score

[a]after 16-weeks patients in the placebo group were assigned to receive open-label tofacitinib 5 mg; [b]all outcomes were pre-specified in the protocol; [c]only discontinuations of study treatment were reported and not discontinuations of study participation.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

A comparative summary for the methodologies of A3921119 and A3921120, are presented in

Figure 7: Participant flow in the A3921120 trial



Source: (51)

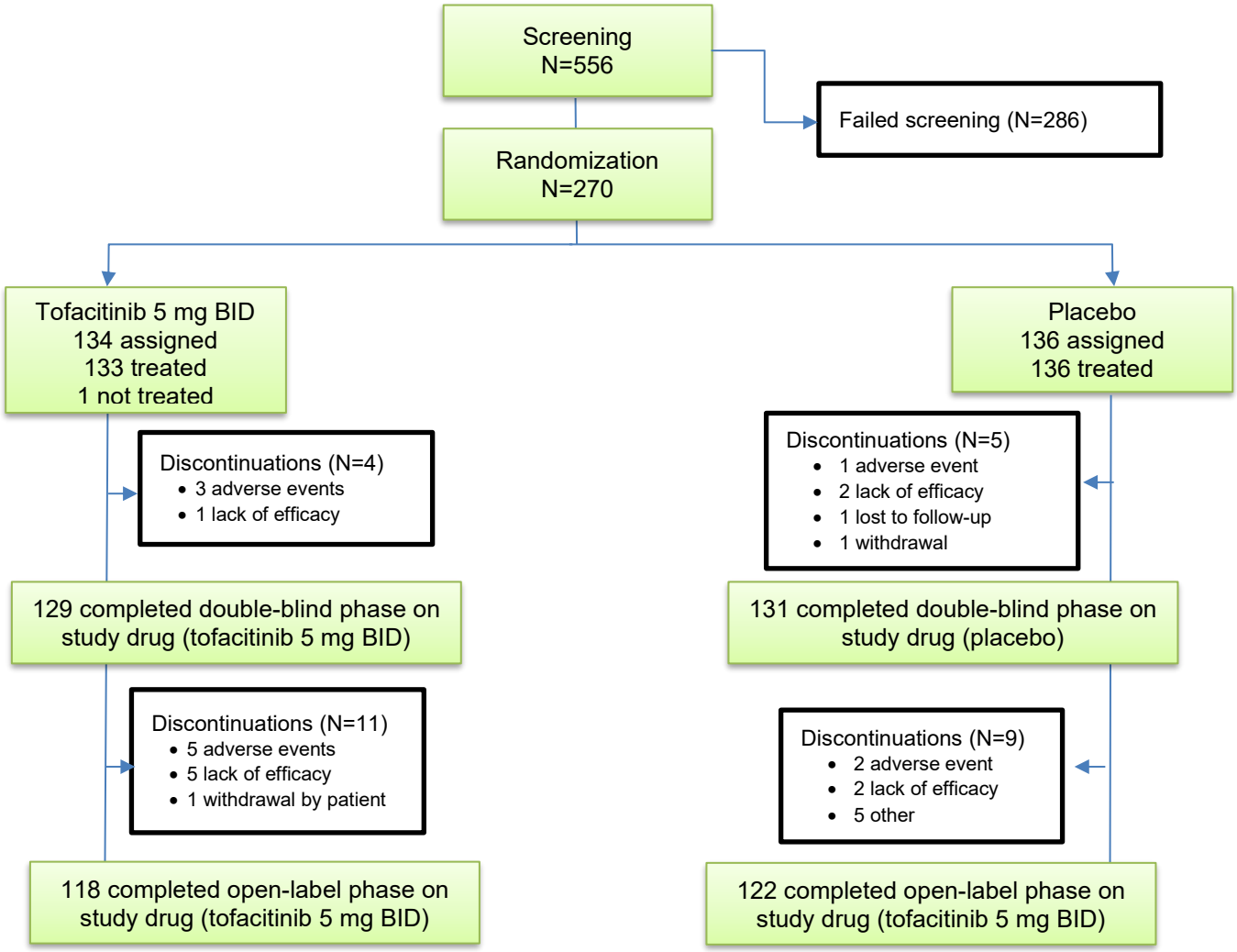
Table 10.

A3921119

A3921119 was a Phase 2, multicentre, double-blind, placebo-controlled, dose-ranging study. It was designed to characterise the dose-response of tofacitinib in adult patients with active AS per New York classification criteria. Eligible patients were randomised in a 1:1:1:1 ratio to receive either tofacitinib 2 mg, 5 mg, or 10 mg BID or placebo for 12 weeks, followed by additional 4-weeks of follow up period. Patients had to have active AS defined as BASDAI score of ≥4 and back pain score (BASDAI Question 2) of ≥4 despite treatment with NSAIDs (or intolerance to NSAIDs). Eleven patients

discontinued. The primary efficacy endpoint was ASAS20 response rate at 12 weeks of treatment (

Figure 7: Participant flow in the A3921120 trial

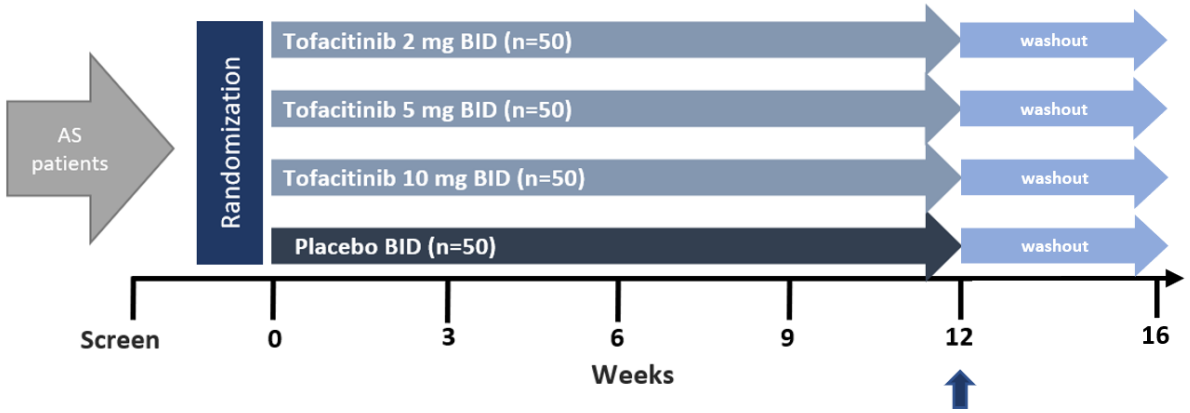


Source: (51)

Table 10; Figure 4). Of 445 patients screened for entry into the study, 208 patients were randomized to double-blind treatment; 52 patients to each treatment group (tofacitinib 2 mg BID, tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo (one subject was randomized to placebo but did not receive study drug). There were 207 patients included in the FAS and 196 patients completed the study.

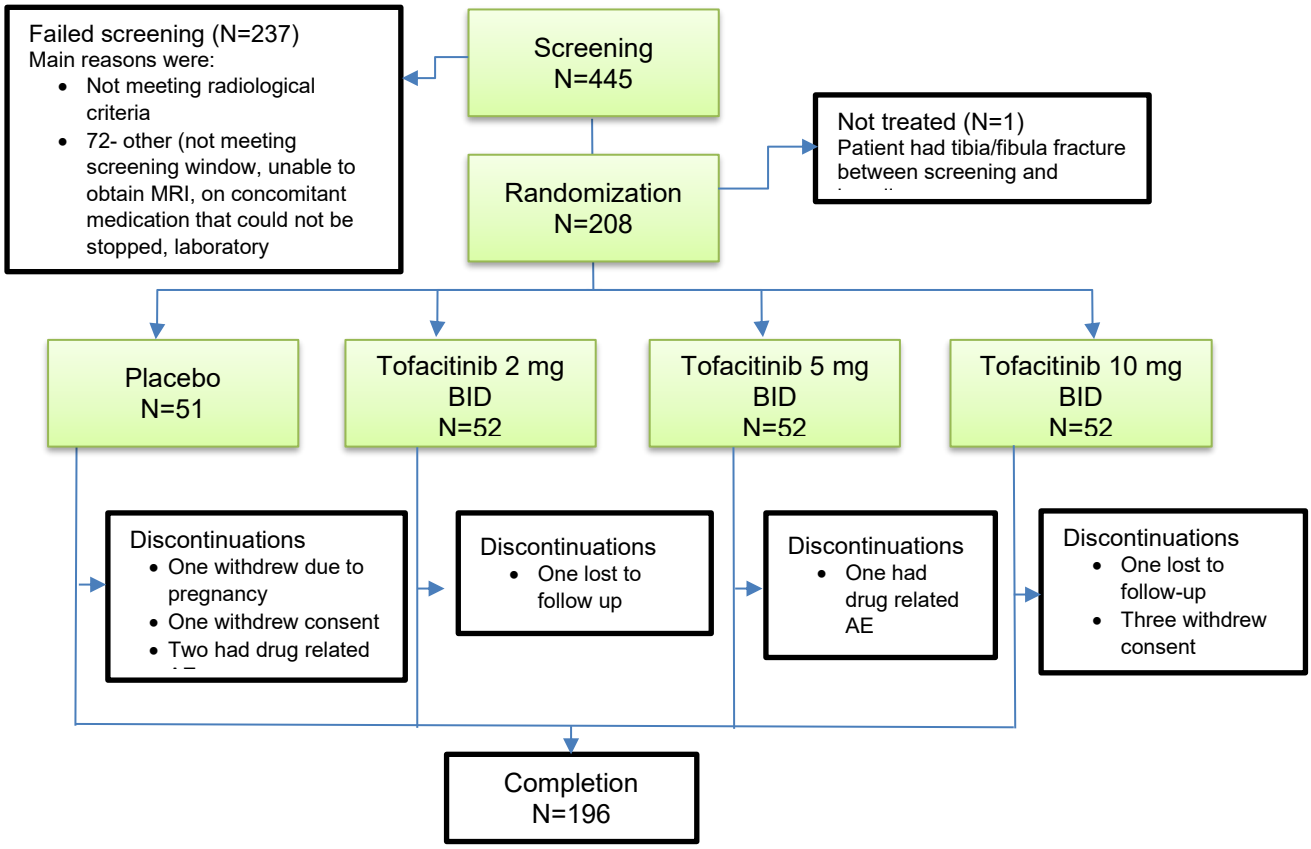
Overall, 11 patients discontinued; four patients withdrew consent (relationship to study drug not defined), four patients (two from placebo group and one subject each from tofacitinib 5 mg BID, and 10 mg BID groups) discontinued due to an AE (related to study drug), two patients were lost to follow-up (relationship to study drug not defined), and one subject discontinued due to pregnancy (**Figure 5**).

Figure 4. Overview of Phase 2 Study Design*



* Desired sample size per cohort determined by clinical trial simulation model
Source: (50)

Figure 5 Participant flow in the A3921119 trial



Source: (50)

A3921120

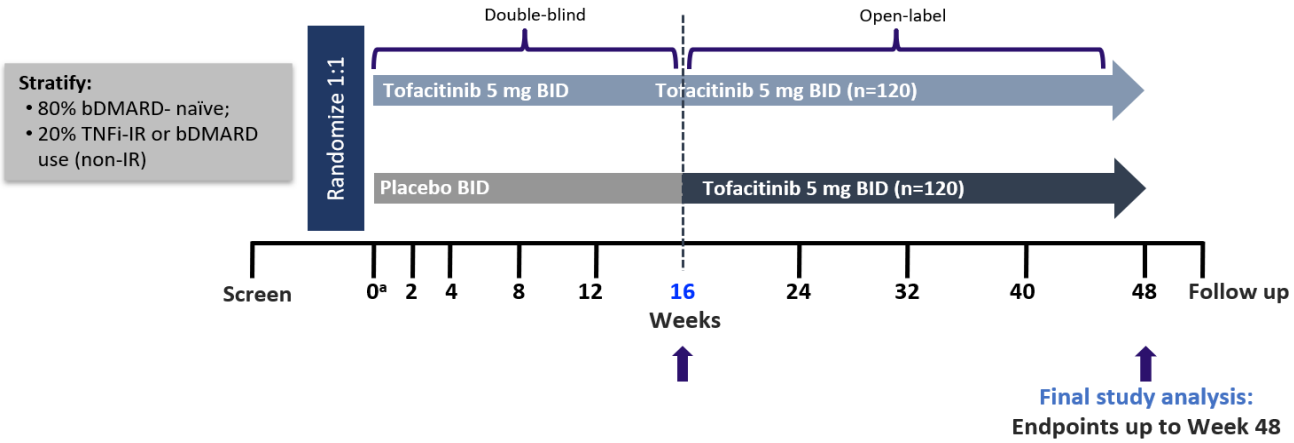
A3921120 was a Phase 3, multicentre, double-blind, placebo-controlled, efficacy and safety study. The study enrolled patients aged 18 years or older with a diagnosis of AS, who met modified New York Criteria, and had an inadequate response or intolerance to two or more NSAID therapies. The primary efficacy endpoint was ASAS20 response rate at 16 weeks of treatment (**Table 10; Figure 6**). Of 556 patients screened for entry into the study, 270 patients were randomized to double-blind treatment; 134 to study drug (one subject was randomized to Tofacitinib group but did not receive study drug), and 136 to receive placebo. There were 269 patients included in the FAS and 240 patients completed the study.

The number of patients that discontinued study drug was similar between the treatment groups; four patients in the tofacitinib 5 mg group and five patients in the placebo group. The majority of patients discontinued study drug due to AEs; three

patients in the tofacitinib 5 mg group and one subject in the placebo group. One subject in the tofacitinib 5 mg group discontinued the study (withdrawal by subject). Three patients in the placebo group discontinued the study; one subject was lost to follow-up and two patients for withdrawal by subject.

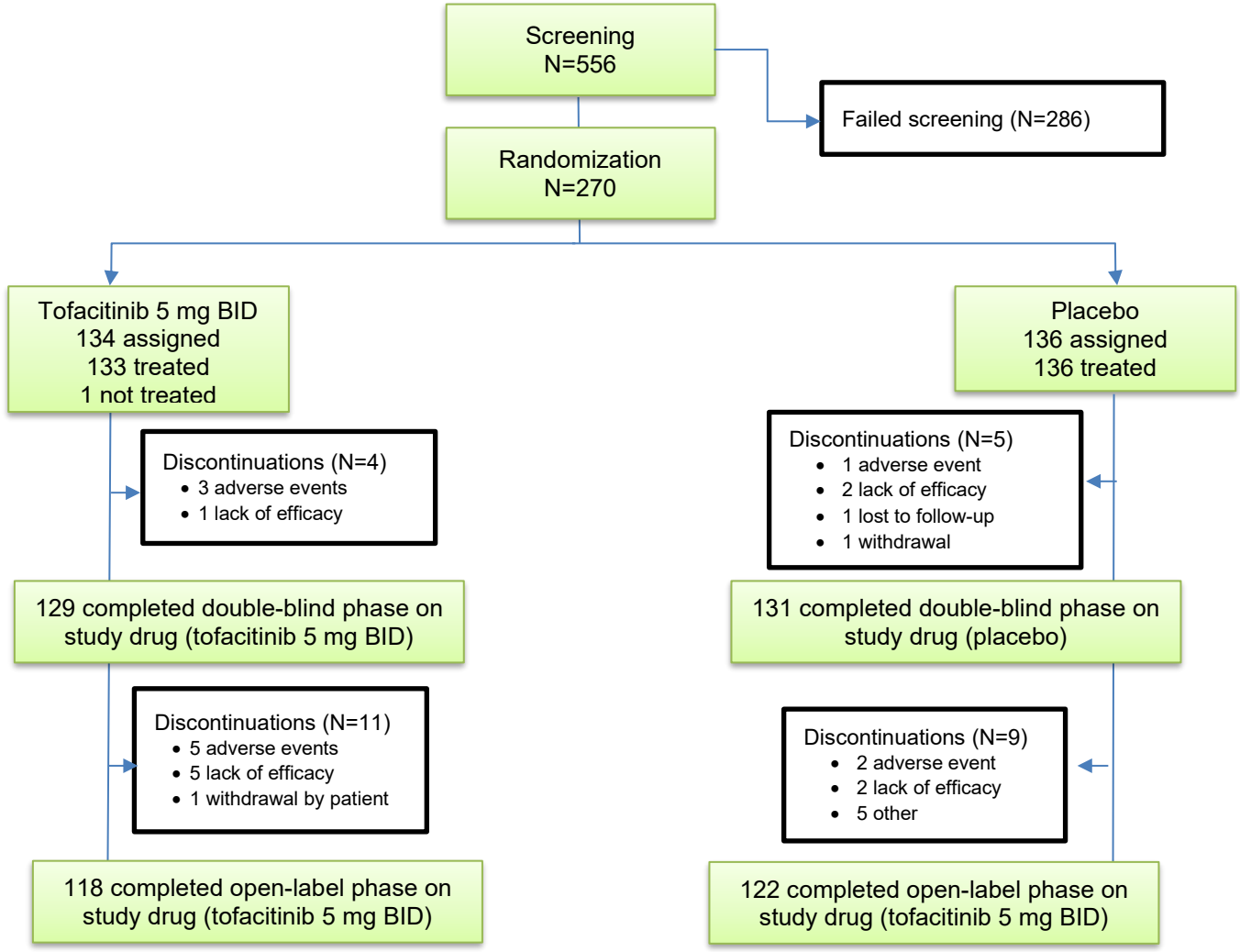
The proportion of patients that discontinued study drug up to Week 48 was higher for tofacitinib 5 mg BID compared to placebo advanced to tofacitinib 5 mg BID. Patients discontinued study drug up to Week 48 in the tofacitinib 5 mg BID group due to AEs (seven patients), lack of efficacy (five patients), and withdrawal by subject (one subject). Patients discontinued study drug in the placebo advanced to tofacitinib 5 mg BID group due to AEs (one subject), lack of efficacy (two patients), lost to follow up (one subject), physician decision (one subject), withdrawal by subject (two patients), and other (two patients). Other reasons included one subject who continued off drug worried from AE (no AE was reported) and one subject who was not willing to continue to take the study drug and stopped taking the drug permanently. **Figure 7**. Eligible patients completing the 16-week double-blind treatment period of the study were assigned to receive open-label tofacitinib 5 mg twice daily for an additional 32 weeks. Patients then entered a 4-week follow-up period in the study.

Figure 6. Overview of Phase 3 Study Design



Source: (51)

Figure 7: Participant flow in the A3921120 trial



Source: (51)

Table 10. A comparative summary of methodologies for the A3921119 and A3921120 tofacitinib trials

Trial number (acronym)	A3921119 (NCT01786668)	A3921120 (NCT03502616)
Duration	16 weeks (12-week treatment period+ 4-week washout period)	48 weeks (16-week double-blind treatment period + 32-week open-label treatment period)
Location	International	International

Trial number (acronym)		A3921119 (NCT01786668)	A3921120 (NCT03502616)
Trial design		A Phase 2, randomised, double-blind, placebo-controlled, dose-ranging, parallel group study	Phase 3, multicentre, randomised, double-blind, placebo-controlled efficacy and safety study
Key eligibility criteria for participants	Inclusion criteria	• Adult patients with AS aged 18 years and older¶ • Diagnosis of AS based on the Modified New York Criteria for Ankylosing Spondylitis (1984). • BASDAI score of ≥ 4 back pain score (BASDAI Question 2) of ≥4 at both screening and baseline • Active disease despite ≥2 NSAID therapy or intolerant to NSAIDs	
	Exclusion criteria	• History of other autoimmune rheumatic disease • Patients requiring prohibited concomitant medications • Patients receiving thalidomide (including previous use)	
		• Patients receiving DMARDs (other than those allowed) • Patients were currently receiving or previous use of a TNFi or other biological agent	• Patients that were exposed to or were receiving targeted synthetic DMARDS (including JAK inhibitors) • Patients on bDMARDS (ie, washout from current bDMARD required)
Settings and locations where the data were collected		10 countries (North America, Europe, Asia) 67 study locations	15 countries (North America, Europe, Australia, Asia) 99 study locations
Trial drugs		Patients (N=208) were randomised to receive: Tofacitinib 2 mg BID (n=52) Tofacitinib 5 mg BID (n=52) Tofacitinib 10 mg BID (n=52) Placebo (n=52)#	Patients (N=270) were randomised to receive: Tofacitinib 5 mg BID (n=134)# Placebo (n=136)*
Concomitant medication	Disallowed	Any DMARDs (synthetic or biologic) except for methotrexate or sulfasalazine Any other investigational or marketed treatment for AS, arthritis or back pain Injected (intravenous, intramuscular, intraarticular or epidural) corticosteroids	

Trial number (acronym)		A3921119 (NCT01786668)	A3921120 (NCT03502616)
	Permitted	Non-biologic DMARDs such as or methotrexate or sulfasalazine NSAIDs, including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) Corticosteroids (except for injected)	
Primary outcomes (including scoring methods and timings of assessments)		ASAS20 response rate at 12 weeks of treatment.	ASAS20 response rate at Week 16.
Key secondary outcomes		NA	ASAS40 response rate at Week 16.
Other outcomes used in the economic model/specified in the scope		• ASDAS-CRP • BASDAI50 • BASDAI† • BASFI • Overall discontinuations • AE-related discontinuations • Serious infections	
Pre-planned subgroups		Analysis of treatment effect (ASAS20 and ASAS40) by composite baseline CRP status	ASAS20 and ASAS40 responses at Week 16 analysed by: • [redacted]

Source: (50-52)

Abbreviations: TNFi, tumor necrosis factor inhibitor; TNFi-IR tumor necrosis factor inhibitor(s)-inadequate responder; CRP, C-Reactive Protein; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; NSAID, non-steroidal anti-inflammatory drugs; DMARD, Disease-modifying antirheumatic drug, bDMARD- biological DMARD

¶ 20 years old for patients in Taiwan in Phase 2 study

* after 16-weeks patients in the placebo group were assigned to receive open-label tofacitinib 5 mg

One subject was randomized but did not receive the study treatment. This subject was excluded from analyses.

† Clinically important (change in BASDAI score of ≥ 0.1 is considered as a clinically meaningful (53))

Baseline demographic, disease and clinical characteristics of patients were generally well-balanced across treatment groups in both studies (see **Table 11**). In both trials there was a greater proportion of male patients in each treatment group, as would be expected in a population of AS patients. The mean age and Body Mass Index (BMI) were generally similar across treatment groups. The majority of patients were white in all treatment groups. Most patients in all treatment groups were HLA-B27 positive. The mean duration since diagnosis of AS was lowest in the tofacitinib 10 mg Phase 2 treatment group (5.4 years [range: 0.0 to 41.7 years]); this treatment group also had the greatest proportion of patients positive for HLA-B27. Mean BASDAI, BASMI and BASFI scored were generally well-balances between the treatment groups in both studies.

Table 11. Baseline demographics and disease characteristics of participants in the studies across treatment groups

Trial number (acronym)	A3921119				A3921120	
Arm	**Tofacitinib 2 mg twice daily N=52**	**Tofacitinib 5 mg twice daily N=52**	**Tofacitinib 10 mg twice daily N=52**	**Placebo N=51**	**Tofacitinib 5 mg BID (N=133)**	**Placebo 5 mg BID (N=136)**
Gender, male, %	65.4	75.0	73.1	62.7	87.2	79.4
Age, years, mean (SD)	41.8 (12.3)	41.2 (10.3)	41.6 (12.2)	41.9 (12.9)	42.2 (11.9)	40.0 (11.1)
BMI, kg/m^2, mean (SD)	26.5 (5.2)	26.3 (4.9)	26.2 (4.4)	27.0 (6.0)	26.7 (5.7)	26.3 (5.8)
Race (%)						
White	75.0	82.7	82.7	84.3	80.5	77.9
Asian	25.0	17.3	17.3	15.7	18.8	22.1
Other	0	0	0	0	0.8	0
HLA-B27 positive (%)	84.6	84.6	94.2	86.3	88.0	86.8
Prior Treatment History, n (%)						
bDMARD-naive	52 (100)	52 (100)	52 (100)	51 (100)	102 (76.7)	105 (77.2)
TNFi-IR or bDMARD Use (Non-IR)	-	-	-	-	31 (23.3)	31 (22.8)

Trial number (acronym)	A3921119				A3921120	
Arm	**Tofacitinib 2 mg twice daily N=52**	**Tofacitinib 5 mg twice daily N=52**	**Tofacitinib 10 mg twice daily N=52**	**Placebo N=51**	**Tofacitinib 5 mg BID (N=133)**	**Placebo 5 mg BID (N=136)**
Median disease duration since diagnosis, years	4.1	3.5	1.5	3.0	[redacted]	[redacted]
BASDAI, mean (SD)	7.0 (1.7)	6.5 (1.9)	6.9 (1.7)	6.3 (1.9)	6.4 (1.5)	6.5 (1.4)
BASFI, mean (SD)	5.5 (1.9)	5.8 (2.2)	5.7 (2.4)	5.7 (2.3)	5.8 (2.3)	5.9 (2.1)
BASMI (Linear-Method), mean (SD)	4.0 (1.7)	3.8 (1.8)	3.9 (2.0)	4.0 (2.0)	4.5 (1.7)	4.4 (1.8)

Source: (51, 52, 54, 55)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; TNFi, Tumour necrosis factor inhibitor; BMI, Body mass index; SD, Standard deviation; bDMARD, biologic disease modifying anti-rheumatic drug; HLA, human leukocyte antigen.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

In the A3921119 Phase 2 trial, [redacted] The primary study objectives were:

- To compare the efficacy of tofacitinib, in doses of 2 mg BID, 5 mg BID, 10 mg BID versus placebo on the ASAS20 response rate at Week 12 in patients with active AS that have had an inadequate response or intolerance to NSAIDs.
- To estimate the placebo-corrected dose response for the ASAS20 at Week 12 in patients with active AS that have had an inadequate response or intolerance to NSAIDs.
- To compare the safety of tofacitinib at all doses versus placebo in all study patients.

The A3921120 Phase 3 trial was designed to prove the superiority of tofacitinib 5 mg BID over placebo for the primary endpoint of ASAS20 at Week 16 (primary objective) and for the key secondary endpoint of ASAS40 at Week 16 (key secondary objective) in patients who have had an active AS and history of either inadequate response or intolerance to NSAID therapy. Patients were to have had an inadequate response or intolerance to at least 2 different oral NSAIDs. In addition, the trial planned to enrol approximately 80% of patients who were bDMARD-naïve and approximately 20% of patients who had an inadequate response or intolerance to at least one but not more than two TNFi's or who were exposed to bDMARDs but without inadequate response (TNFi-IR or bDMARD-experienced (Non-IR)).

Both studies were analysed within two analysis Sets:

- Full Analysis Set (FAS) that included all patients who were randomised to the study and received at least one dose of the randomised study drug (tofacitinib or placebo). The primary efficacy population for the A3921119 and A3921120 studies was defined by the full analysis set of patients.

- Per Protocol Analysis Set (PP) that excluded all patients from the FAS who had at least one protocol deviation thought to have a material impact on the primary efficacy analysis.

An overview of statistical methods implemented in both tofacitinib studies is presented in the Table 12.

Table 12. Summary of statistical analyses

Trial	**A3921119 (NCT01786668)**
Duration	16 weeks (12-week treatment period+ 4-week washout period)
Hypothesis	[redacted]
Statistical analysis	The primary efficacy analysis used the FAS. A three parameter Emax model was used to estimate the 60% and 50% credible intervals. As a supportive analysis, the normal approximation for estimating the difference in binomial proportion All analysis was also conducted on the PP analysis set since the FAS may include instances of non-c

Trial	A3921119 (NCT01786668)

Trial	A3921119 (NCT01786668)

Trial	A3921119 (NCT01786668)
Sample size, power calculation	Sample size was assessed using clinical trial simulations (CTS) in which a dose-response model (the 20-40%, then it was projected that the estimated placebo-corrected effect for that dose—plus or minu
Data management, patient withdrawals	[redacted]

Trial	A3921119 (NCT01786668)

Source: (56),(52)

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI, Work Productivity and Activity Impairment; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score Using C-Reactive Protein; EQ-VAS, EuroQol Visual Analogue Scale; AEs, adverse events; ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; EQ-5D, EuroQol 5-dimensions questionnaire; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID, non-steroidal anti-inflammatory drugs; SF-36v2, 36-Item Short Form Survey version 2.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

Both trials were conducted in accordance with good clinical practice (GCP) guidelines with a single protocol to promote consistency across sites, and with measures taken to minimise bias. The accuracy and reliability of the clinical study data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the sponsor.

Randomisation in the trials was successfully carried out such that baseline demographics and disease characteristics were generally similar between groups and typical of an active AS population. Patients and investigators remained blinded throughout the study, and all outcome assessments were conducted in accordance with Full Analysis Set principle.

Discontinuation rates were low. The number of patients that discontinued study drug was similar between the treatment group(s) and the placebo group. Patient withdrawals were accounted for with pre-defined, censoring methods.

A quality assessment adapted from CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination) was undertaken to provide more information about the quality of this research subset on what is viewed as the highest level of evidence. The methodologic quality was assessed using seven categories of potential bias (Table 13). The risk of bias in both trials is considered to be low (**see Appendix D**).

Table 13. Quality assessment results for parallel group RCTs

Trial number (acronym)	A3921119 (NCT01786668)	A3921120 (NCT03502616)
Was randomization carried out appropriately?	yes	yes
Was the concealment of treatment allocation adequate?	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	yes	yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	yes	yes
Were there any unexpected imbalances in dropouts between groups?	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	no
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	yes	yes

B.3.6 Clinical effectiveness results of the relevant trials

The data discussed in this section has been sourced from the Phase 2 and Phase 3 tofacitinib trials A3921119 and A3921120. Data are taken from primary publications (50, 51) and supplemented with data from clinical study reports (52, 56).

The A3921119 and A3921120 trials sought to investigate the key clinical outcomes described below and in the decision problem:

1. Disease activity outcomes

- ASAS20
- ASAS40
- BASDAI50
- Change from baseline in ASDAS-CRP
- ASDAS-CRP major improvement
- Change from baseline in BASDAI
- Change from baseline in BASMI

2. Functional capacity
   - Change from baseline in BASFI
3. Pain
   - Change from baseline in Total Back Pain
   - Change from baseline in Nocturnal Spinal Pain
4. Peripheral symptoms
   - MASES
5. HRQoL outcomes, including:
   - Change from baseline in ASQoL
   - Change from baseline in SF-36v2 (mental and physical summary components)
   - Change from baseline in FACIT-F Total score

Additionally, change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Index of Disease Activity Score and change from baseline in High Sensitivity C-Reactive Protein (hsCRP) score are presented in the submission.

Safety outcomes specified in the decision problem are addressed in the Section B3.10.

B.3.6.1 Dose selection rationale

In Phase 2 study A3921119, ASAS20 response rate after tofacitinib 5 mg BID was significantly higher than placebo; tofacitinib 2 mg and 10 mg BID demonstrated greater response rate than placebo but were not significant. A consistent magnitude of efficacy was not observed after the lowest dose (2 mg BID) of tofacitinib, especially with more objective endpoints. Compared to 5 mg BID, the 10 mg tofacitinib dose did not

demonstrate consistent or clinically meaningful additional improvements in efficacy across study endpoints.

Tofacitinib 5 mg BID is the dose approved by the EMA for use in rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

Given the results of the Phase 2 study of tofacitinib in AS patients as well as taking into consideration the current BID posology for tofacitinib in other rheumatologic diseases, 5 mg BID of tofacitinib was selected to be evaluated in the Phase 3 study in AS patients. Consequently, Phase 2 results for 2 mg BID and 10 mg BID are omitted in the core document and presented in **Appendix I**.

B.3.6.2 A3921119 (Phase 2)

A summary of efficacy outcomes (disease activity, functional capacity, pain and peripheral symptoms) at Week 12, reported in this submission, can be found in Table 14 (50, 56).

Disease Activity

ASAS20

The primary analysis of the ASAS20 response rate at Week 12 was conducted on the FAS using an Emax model with missing response as non-response. The estimated response rates were 40.1% for placebo and 63.0% for tofacitinib 5mg BID, demonstrating that the response rate for tofacitinib was higher than for placebo.

The ASAS20 actual response rate at Week 12 with missing response as non-response was greater in the tofacitinib 5 mg BID treatment group (80.8%), than in placebo group (41.2%) and the difference was statistically significant ($p<0.001$).

ASAS40

At Week 12, there was a statistically significant higher ASAS40 response rate for tofacitinib 5 mg BID treatment group (46.2%) compared with placebo (19.6%; p=[redacted]).

ASDAS-CRP major improvement rate

Tofacitinib 5 mg BID had a greater response rate for ASDAS-CRP major improvement rate (defined as decrease from baseline of ≥2 units) compared to placebo treatment group at Week 12 (23.1% vs 11.8%, respectively); [redacted].

Change from baseline in ASDAS-CRP score

A comparison of ASDAS-CRP score at Week 12 showed a statistically significant improvement from baseline in the LS mean ASDAS values for tofacitinib 5 mg BID treatment group compared with the placebo treatment group (-1.4 vs. -0.7 respectively; [redacted]).

BASDAI50

At Week 12, there was a statistically significant greater BASDAI50 response rate for tofacitinib 5 mg BID treatment group than placebo (p=[redacted]). BASDAI50 response rates were 42.3% compared with 23.5% for the placebo treatment group.

Change from baseline in BASDAI score

At Week 12, there was a statistically significant greater improvement in Least Squares (LS) mean BASDAI values for tofacitinib 5 mg BID group (-2.9) compared with the placebo treatment group (-1.9; p=[redacted]).

Change from baseline in BASMI score

At Week 12, there was a greater LS mean improvement (decrease) from Baseline for the BASMI values in 5 mg BID tofacitinib treatment group (−0.4) than in placebo group (−0.2). The difference was not statistically significant (p=[redacted]).

Functional capacity

Change from baseline in BASFI score

By Week 12 tofacitinib 5 mg BID treatment group had a greater mean improvement from Baseline in BASFI score than the placebo treatment group (-2.4 vs -1.4, respectively). The improvement was statistically significant (p=[redacted]).

Pain

Change from baseline in total back pain score

By Week 12 patients in tofacitinib 5 mg BID treatment group had a greater mean improvement from Baseline in total spinal pain than the placebo treatment group ([redacted]).

Change from baseline in Nocturnal spinal pain score

The negative mean change from Baseline at Week 12 showed greater improvement from Baseline for tofacitinib 5 mg BID treatment group ([redacted]) than for the placebo treatment group ([redacted]).

Peripheral symptoms

Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) score

At Week 12, there was a statistically significant greater improvement (decrease) from Baseline for the LS mean MASES scores for the tofacitinib 5 mg BID treatment group as compared to placebo ([redacted]).

MRI endpoints

Change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Index of Disease Activity Score

At Week 12, there was a statistically significant greater improvement from baseline for the tofacitinib 5 mg as compared to placebo in the LS mean SPARCC measure, both for Sacroiliac Joints score ([redacted] difference with p=[redacted]) as well as Spine score ([redacted] difference with p<0.001).

Table 14. Summary of efficacy outcomes (disease activity, functional capacity, pain, peripheral symptoms and MRI endpoints) at week 12 in A3921119 (Full Analysis Set)

	Tofacitinib 5 mg BID N=52	Placebo N=51	Difference (95% CI)	P value
PRIMARY EFFICACY ENDPOINT				
Disease activity				
Emax model predicted ASAS20 response, %	63.0	40.1	22.9 (8.4, 37.7*)	NR
ASAS20, actual response, % (SE)	80.8 ([redacted])	41.2 ([redacted])	[redacted]	<.001
SECONDARY EFFICACY ENDPOINTS				
Disease activity				
ASAS40, response, %	46.2 ([redacted])	19.6 ([redacted])	[redacted]	[redacted]
ASDAS-CRP Major Improvement, % (SE)	23.1 ([redacted])	11.8 ([redacted])	[redacted]	[redacted]
Δ ASDAS-CRP, LS mean (SE)	-1.4 (0.1)	-0.7 (0.1)	[redacted]	[redacted]
BASDAI50, response, %	42.3 ([redacted])	23.5 ([redacted])	[redacted]	[redacted]
Δ BASDAI, LS mean (SE)	−2.9 (0.3)	−1.9 (0.3)	[redacted]	[redacted]
Δ BASMI, LS mean (SE)	−0.42 (0.1)	−0.16 (0.1)	[redacted]	[redacted]
Functional capacity				
Δ BASFI, LS mean (SE)	−2.4 (0.3)	−1.4 (0.3)	[redacted]	[redacted]
Pain				
Δ Total back pain±, mean, (SD)	[redacted]	[redacted]	na	na
Δ Nocturnal spinal pain, mean±, (SD)	[redacted]	[redacted]	na	na

	Tofacitinib 5 mg BID N=52	Placebo N=51	Difference (95% CI)	P value
Peripheral symptoms				
Δ MASES, LS mean, (SE)	[redacted]	[redacted]	[redacted]	[redacted]
MRI endpoints				
SPARCC Score of Sacroiliac Joints	-3.2 (0.8)	-0.8 (0.8)	-2.4 (-4.6, -0.1)	0.04
SPARCC Score of the Spine	-5.51 (1.1)	-0.09 (1.1)	[redacted]	<.001

Source: (50, 56)

Abbreviations: LS-Least Squares, SE-Standard Error; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; na-not applicable, SPARCC- Spondyloarthritis Research Consortium of Canada

± descriptive data.

Quality of life outcomes

A summary of Quality of Life outcomes can be found in Table 15.

Change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) score

Using an ANCOVA model at Week 12, there was a statistically significantly greater improvement (decrease) from Baseline for the LS mean ASQoL score for the tofacitinib 5 mg BID treatment (-4.8), compared to placebo group (-2.5; p=[redacted]).

Change from baseline in Short Form-36 Health Survey (SF-36v2) version 2 score

Using an ANCOVA model at Week 12, there was a statistically significant greater improvement (increase) from Baseline for the LS mean Physical Health Component Score for the tofacitinib 5 mg BID (6.5) compared to placebo (2.7; p=[redacted]).

Using an ANCOVA model at Week 12, there were no statistically significant difference in the change from Baseline for the LS mean Mental Health Component Score between the tofacitinib 5 mg BID group and the placebo treatment group (p>0.05). However, LS mean increase from baseline was numerically greater in the tofacitinib 5 mg BID (4.2) compared to the placebo treatment group (2.4).

Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score

The LS mean increase from baseline in FACIT-F total score demonstrated a statistically significant difference for tofacitinib 5 mg BID from placebo at Week 12 (p = [redacted]).

Table 15. Quality of life outcomes using ANCOVA model at Week 12 from A3921119 (Full Analysis Set)

	Tofacitinib 5 mg BID N=52	Placebo N=51	Difference (95% CI)	P value
Ankylosing Spondylitis Quality of Life				
Δ ASQoL Total Score, LS mean (SE)*	-4.8 (0.6)	-2.5 (0.6)	[redacted]	[redacted]
Short Form-36 Health Survey version 2				
Δ SF-36v2 Physical Component Summary Score, LS mean (SE)	6.5 (0.9)	2.7 (0.9)	[redacted]	[redacted]
Δ SF-36v2 Mental Component Summary Score, LS mean (SE)	4.1 (1.3)	2.4 (1.3)	[redacted]	[redacted]
Functional Assessment of Chronic Illness Therapy-Fatigue				
Δ FACIT-F Total Score, LS mean (SE)	7.0 (1.1)	3.1 (1.2)	[redacted]	[redacted]

Source: (50, 56)
*In the case of ASQoL, decrease from baseline indicates improvement in QoL.
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ASQoL, Ankylosing Spondylitis Quality of Life; SF-36v2, 36-Item Short Form Survey version 2.

B.3.6.3 A3921120 (Phase 3)- efficacy at Week 16 (Primary Analysis)

A summary of efficacy outcomes (disease activity, functional capacity, pain, peripheral symptoms and hsCRP) at Week 16, reported in this submission, can be found in Table 16 (51, 52).

Disease Activity

ASAS20 *(Global Type I error-controlled endpoint)*

The study met the primary efficacy endpoint, tofacitinib 5 mg BID demonstrated superiority over placebo in ASAS20 response at Week 16 (56.4% vs 29.4% respectively, p <0.0001).

ASAS40 *(Global Type I error-controlled endpoint)*

The observed ASAS40 response rate (key secondary endpoint) at Week 16 was greater in the tofacitinib 5 mg BID treatment group (40.6%) than in placebo group (12.5%), and the difference was statistically significant (p<0.001).

ASDAS-CRP major improvement rate *(Non-Type I error-controlled endpoint)*

The ASDAS-CRP major improvement response rate (defined as decrease from baseline of ≥2.0 for patients with baseline ASDAS(CRP) ≥2.636 for tofacitinib 5 mg BID was significantly greater compared to placebo at Week 16 ([redacted]).

BASDAI50 *(Non-Type I error-controlled endpoint)*

At Week 16, there was a statistically significant (p<0.0001) higher BASDAI50 response rate for tofacitinib treatment group (42.8%) compared with placebo (17.6%).

Change from baseline in ASDAS-CRP score *(Global Type I error-controlled endpoint)*

Improvement in ASDAS-CRP of tofacitinib 5 mg BID was greater than that of placebo at Week 16 (-1.4 vs -0.4, respectively) and the difference was statistically significant (p<0.0001).

Change from baseline in BASDAI score *(Non-Type I error-controlled endpoint)*

Improvement in BASDAI of tofacitinib 5 mg BID was greater than that of placebo at Week 16 (-2.5 vs -1.1, respectively) and the difference was statically significant (p<0.0001).

Change from baseline in BASMI score *(Global Type I error-controlled endpoint)*

At Week 16, there was a statistically significant greater LS mean improvement (decrease) from Baseline for the BASMI values in tofacitinib group (-0.63) compared to placebo (-0.11, p<0.0001).

Functional capacity

Change from baseline in BASFI score *(Type I error-controlled endpoint)*

The LS mean change from baseline in BASFI showed statistically significant decreases for the tofacitinib 5 mg BID (-2.0) compared to placebo (-0.8) at Week 16 (p <0.0001).

Pain

Change from baseline in Total back pain score *(Type I error-controlled endpoint)*

At Week 16, the LS mean change from baseline for Total Back Pain showed statistically significant decreases for the tofacitinib 5 mg BID (-2.6) compared to placebo (-1.0; p <0.0001).

Change from baseline in Nocturnal Spinal Pain score *(Non-Type I error-controlled endpoint)*

The LS mean decreases from baseline in nocturnal spinal pain were greater for tofacitinib 5 mg BID ([redacted]) compared to placebo ([redacted]) based on MMRM beginning at Week 16. Difference was statistically significant ([redacted]).

Peripheral symptoms

Change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) *(Non-Type I Error-Controlled Endpoint)*

No statistically significant difference in LS mean change from baseline in MASES was observed between tofacitinib 5 mg BID (-1.94) and placebo (-1.41) at Week 16.

sCRP level: Change from baseline in High Sensitivity C-Reactive Protein (hsCRP) score *(Type I error-controlled endpoint)*

The LS mean change from baseline in hsCRP showed statistically significant decreases for tofacitinib 5 mg BID compared to placebo at Week 16 (-1.0 vs -0.1; p <0.0001).

Table 16. Summary of efficacy outcomes at Week 16 in A3921120 (Full Analysis Set)

	Tofacitinib 5 mg twice daily N=133	**Placebo N=136**	**Difference (95% CI)**	**P value**
PRIMARY EFFICACY ENDPOINT				
Disease activity				
ASAS20, response, %	56.4	29.4	[redacted]	<.0001
KEY SECONDARY EFFICACY ENDPOINT				
Disease activity				
ASAS40, response, %	40.6	12.5	[redacted]	<.0001
SECONDARY EFFICACY ENDPOINTS				
Disease activity				
ASDAS-CRP Major Improvement, %	30.1	4.7	[redacted]	<.0001
BASDAI50, response, %	42.9	17.7	[redacted]	<.0001
Δ ASDAS-CRP, LS mean (SE)	-1.5 (0.08)	-0.4 (0.08)	[redacted]	<.0001
Δ BASDAI, LS mean (SE)	-2.6 (0.2)	-1.1 (0.2)	[redacted]	<.0001
Δ BASMI, LS mean (SE)	-0.6 (0.06)	-0.1 (0.06)	[redacted]	<.0001
Functional capacity				

	Tofacitinib 5 mg twice daily N=133	Placebo N=136	Difference (95% CI)	P value
Δ BASFI, LS mean (SE)	-2.1 (0.2)	-0.8 (0.2)	[redacted]	<.0001
Pain				
Δ Total back pain, LS mean, (SE)	-2.6 (0.2)	-1.0 (0.2)	[redacted]	<.0001
Nocturnal spinal pain, LS mean, (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral symptoms				
Δ MASES, LS mean, (SE)	-1.9 (0.3)	-1.4 (0.3)	[redacted]	[redacted]
HsCRP level				
Δ hsCRP, LS mean (SE)	-1.1 (0.1)	-0.1 (0.1)	[redacted]	<.0001

Source: (51, 52)
Abbreviations: LS-Least Squares, SE-Standard Error; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; na-not applicable

Quality of life outcomes

A summary of Quality of Life outcomes can be found in Table 17.

Change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) score *(Global Type I error-controlled endpoint)*

Using an ANCOVA model at Week 16, there was a statistically significant greater LS mean decrease from baseline in ASQoL for tofacitinib 5 mg BID compared to placebo (-4.0 vs -2.0 respectively; p=0.0001)

Change from baseline in Short Form-36 Health Survey (SF-36v2) Physical Component Summary score *(Global Type I error-controlled endpoint)*

Using an ANCOVA model at Week 16 there was a statistically significant greater improvement (increase) from Baseline for the LS mean Physical Component Summary for the tofacitinib 5 mg BID (6.7), compared to placebo (3.1; p<.0001).

Change from baseline in Short Form-36 Health Survey (SF-36v2) Mental Component Summary score *(Non-Type I error-controlled endpoint)*

Using an ANCOVA model at Week 16, there were [redacted] the change from Baseline for the LS mean Mental Component Summary between the tofacitinib treatment group and the placebo treatment group ([redacted]). LS mean increase from Baseline in Mental Component Summary was greater in the tofacitinib 5 mg BID group ([redacted]) comparing to the placebo treatment group ([redacted]).

Change from baseline in Short Form-36 Health Survey (SF-36v2) Social Functioning domain score *(Non-Type I error-controlled endpoint)*

Using an ANCOVA model at Week 16, [redacted] Baseline for the LS mean Social Functioning domain score for the tofacitinib 5 mg BID ([redacted]) compared to placebo ([redacted]).

Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score *(Global Type I error-controlled endpoint)*

Based on mixed model for repeated measures (MMRM), The LS mean increase from baseline in FACIT-F total score demonstrated a statistically significant difference for tofacitinib 5 mg BID (6.54) from placebo (3.12) at Week 16 (p=0.0008).

Table 17. Quality of life outcomes from Phase 3 trial at 16 weeks (Full Analysis Set)

	Tofacitinib 5 mg BID N=133	Placebo N=136	Difference (95% CI)	P value
Ankylosing Spondylitis Quality of Life**				
Δ ASQoL Total Score, LS mean (SE)	-4.0	-2.0	[redacted]	0.0001
Short Form-36v2 Health Survey**				
Δ SF-36v2 Physical Component Summary Score model, LS mean (SE)	6.7 (0.6)	3.1 (0.6)	[redacted]	<.0001
Δ SF-36v2 Mental Component Summary Score, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Δ SF-36v2, Social Functioning domain, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***Functional Assessment of Chronic Illness Therapy-Fatigue*±				
Δ FACIT-F Total Score, LS mean (SE)	6.5 (0.8)	3.1 (0.8)	[redacted]	0.0008

Source: (51, 52)
*In the case of ASQoL, decrease from baseline indicates improvement in QoL.
** using ANCOVA model, ±based on MMRM
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; ASQoL, Ankylosing Spondylitis Quality of Life; SF-36v2, 36-Item Short Form Survey version 2
*using ANCOVA model, ±based on MMRM

B.3.6.4 A3921120 (Phase 3) - efficacy before Week 16

Two weeks after treatment initiation with tofacitinib 5mg BID, patients showed a significant reduction in disease activity measured by ASAS20 compared with

placebo (with the response of 28.6% and 10.3% in the tofacitinib and placebo group respectively; [redacted]).

Tofacitinib also demonstrated early onset of efficacy in terms of back pain, which was significantly reduced at 2 weeks in treatment group compared to placebo group (-1.3 vs -0.4 respectively; [redacted]) (**Error! Reference source not found.**).

Table 18. Summary of early efficacy outcomes (2-Weeks data) in A3921120 (Full Analysis Set)

	Tofacitinib 5 mg twice daily N=133	**Placebo N=136**	**Difference (95% CI)**	**P value**
Disease activity				
ASAS20, response[a], %	28.6	10.3	[redacted]	[redacted]
Pain				
Δ Total back pain[b], LS mean, (SE)	-1.3 [redacted]	-0.4 [redacted]	[redacted]	[redacted]

Source: (51, 52)
Abbreviations: LS-Least Squares, SE-Standard Error; ASAS- Assessment of Spondyloarthritis International Society
[a]CMH Normal Approximation, On-Drug Data, MR=NR
[b]MMRM Analysis, On-Drug Data, No imputation

B.3.6.5 A3921120 (Phase 3)- efficacy up to Week 48

To assess the long-term efficacy of tofacitinib, patients were monitored and assessed up to Week 48. Importantly, the efficacy of ASAS20, ASAS40, ADSAS(CRP) and BASDAI50 response observed for tofacitinib at Week 16 were consistently sustained through to Week 48. Increased response rates were also observed in patients from initial placebo group who advanced to tofacitinib 5 mg BID in open-label study period. (**Table 19**).

Table 19. Key Primary and Secondary Efficacy Endpoints at Week 16 and Week 48 in A3921120 (Full Analysis Set)

	Week 16 (16-week data cut-off)		Week 48 (48-week final data)	
	Tofacitinib 5 mg BID N=133	**Placebo N=136**	**Tofacitinib 5 mg BID N=133**	**Placebo -> Tofacitinib 5 mg BID N=136**
ASAS20 response	56.4%	29.4%	65.4%	60.3%
ASAS40 response	40.6%	12.5%	50.4%	44.9%
ASDAS-CRP Major Improvement response	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50 response	42.8%	17.6%	51.1%	40.4%

Source: (51, 57)
Data presented at week 16 come from the Week 16 database analysis and the data presented at week 48 come from the Week 48 final analysis
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index;

B.3.7 Subgroup analysis

Pre-defined subgroup comparisons for ASAS20 and ASAS40 responses at Week 16 were made on the FAS with missing values handled by "missing response as non-response" approach. The efficacy of tofacitinib 5 mg BID for [redacted]

The efficacy of tofacitinib 5 mg BID for ASAS40 responses at Week 16 [redacted]

[redacted]

For the full list of pre-defined subgroups see Table 10.

Tofacitinib was also consistently efficacious across subgroups of prior treatment history (bDMARD naïve and TNFi-IR or bDMARD use [Non-IR]), as assessed by ASAS20 and ASAS40 response rates (**Table 20**).

Table 20 Subgroup Analysis of ASAS20 and ASAS40 Response Rates at Week 16 in A3921120 (Full Analysis Set)

	Tofacitinib 5 mg twice daily	Placebo	Difference (95% CI)	P value
ASAS20, response, %				
All patients N=269	56.4	29.4	[redacted]	<.0001
bDMARD naïve N=207	61.8	33.3	[redacted]	-
TNFi-IR or bDMARD use [Non-IR] N=62	38.7	16.1	[redacted]	-
ASAS40, response, %				
All patients N=269	40.6	12.5	[redacted]	<.0001
bDMARD naïve N=207	45.1	14.3	[redacted]	-
TNFi-IR or bDMARD use [Non-IR] N=62	25.8	6.5	[redacted]	-

Source: (51, 52)

Abbreviations: TNFi-IR tumor necrosis factor inhibitor(s)-inadequate responder; ASAS, Assessment of Spondyloarthritis International Society; bDMARD- biological Disease-modifying antirheumatic drug

B.3.8 Meta-analysis

No meta-analysis of the A3921119 and A3921120 studies alone was performed. An NMA was conducted to estimate the relative effectiveness of tofacitinib 5 mg BID mg and relevant comparator therapy, adalimumab and both the A3921119 and A3921120 studies were included (see Section B.3.9).

B.3.9 Indirect and mixed treatment comparisons

The SLR (**Appendix D**) did not identify any available direct evidence comparing tofacitinib 5 mg BID with adalimumab. Therefore, an NMA was performed to evaluate the relative efficacy and safety of tofacitinib compared to this treatment. The primary objective of the NMA was to compare the efficacy and safety of tofacitinib 5 mg BID against adalimumab 40 mg Q2W for the treatment of AS. This represents the population of relevance to the decision problem outlined in this submission.

B.3.9.1 Methods

The full methodology of the SLR conducted to inform the NMA is described in **Appendix D**. A total of 72 RCT articles were identified in the SLR and eight (out of nine) were retained for the NMA. A single site trial of 40 mg adalimumab (n=26) vs placebo (n=20) in China was excluded from the base-case NMA analysis due to a high risk of bias (58):

- No data on attrition were included in the trial
- Primary outcomes were not stated, and only selected efficacy outcomes were reported in the publication
- Insufficient details on random sequence generation, allocation concealment, and blinding of participants.

A list of articles included in the SLR and those that were included and excluded in the NMA along with the rationale is provided in **Appendix D**.

Clinical outcomes for evaluation in the NMA were selected based on outcomes used in the CE models of previous appraisals: TA383, TA407, TA718 (see Section B2). Outcomes considered relevant for this submission were: ASAS20, ASAS40, BASDAI50, BASDAI, BASFI, and BASMI, reported at timepoints between Week 12 – 16. In addition to clinical endpoints, the QoL endpoints were selected to address one generic scale (SF-36v2) and one disease-specific scale (ASQoL).

For each study, 12-16-week data were extracted and analysed, providing that data represented outcomes reported during the placebo-controlled period. Where exact

values were not reported within each study, graphs from each of the studies, where available, were digitized to obtain the necessary data. Where specific patient counts were not reported, the percentage of patients with each outcome was used to calculate patient counts. Counts were recorded from an ITT perspective; therefore, patients that dropped out were counted as non-responders for each outcome. Only outcomes during the placebo-controlled period were considered.

Studies were then analysed, and 2 subpopulations were identified according to previous bDMARD/TNFi exposure (mixed population vs only treatment-naïve patients) for treatment efficacy and QoL outcomes. The analysis was conducted from a Bayesian perspective using WinBUGS. Non-informative prior distributions were assumed. Convergence was assessed by running 3 chains using the Gelman Rubin Statistic. Both fixed and random effect models were fitted and the goodness of fit was determined using the deviance information criterion (DIC). Where feasible, baseline-risk adjusted fixed and random effects were also performed. WinBUGS codes from NICE TSD 2 and 3 were adapted to conduct the analysis within WinBUGS (59, 60). Full details on NMA synthesis methods as well as the Risk of Bias assessment can be found in the **Appendix D**.

B.3.9.2 Results

Studies varied in their double-blind periods, from 12 to 16 weeks. All studies included in the NMA used the modified New York criteria to identify patients with active AS. Patient characteristics were generally similar, especially with respect to disease activity measured by BASDAI. Adalimumab trials included in this NMA were also previously included in TA383 (except COAST-V which was released after TA383) and all were deemed generalisable to clinical practice in the UK. From the adalimumab trials, one study was excluded from base-case analysis of two outcomes (BASDAI change from baseline and BASFI change from baseline) due to a high risk of bias (58). Full baseline characteristics of all trials are provided in the **Appendix D**.

For all endpoints, Bayesian models for fixed effects (FE) and random effects (RE) were considered. RE models were selected for presentation in Document B due to substantial heterogeneity for some outcomes (see **Appendix D**) and as it has previously been recommended for interpreting outcomes of NMAs with fewer than 10

studies when the DIC is comparable between the models (see **Justification for Random Effects Model**). FE model outcomes are available in **Appendix D**. Due to significant convergence, baseline unadjusted results are presented.

Error! Reference source not found. provides an overall summary of tofacitinib versus each relevant comparator, for each evaluated outcome, in the mixed population as well as biologic-naïve population. Detailed results of the relative comparisons are then presented in the following sections.

Table 21: Overall summary of significance or non-significance of relative comparisons of Tofacitinib mg versus comparators (Random Effects without baseline adjustments[a])

		PBO	ADA
Mixed population			
ASAS20	**TOF**	[redacted]	[redacted]
ASAS40	**TOF**	[redacted]	[redacted]
BASDAI50	**TOF**	[redacted]	[redacted]
Δ BASDAI	**TOF**	[redacted]	[redacted]
Δ BASFI	**TOF**	[redacted]	[redacted]
Δ BASMI	**TOF**	[redacted]	[redacted]
Δ ASQoL[b]	**TOF**	[redacted]	[redacted]
Δ SF36 PCS	**TOF**	[redacted]	[redacted]
Δ SF36 MCS	**TOF**	[redacted]	[redacted]
Treatment-Naïve Population			
ASAS20	**TOF**	[redacted]	[redacted]
ASAS40	**TOF**	[redacted]	[redacted]
BASDAI50	**TOF**	[redacted]	[redacted]
Δ BASDAI	**TOF**	[redacted]	[redacted]
Δ BASFI	**TOF**	[redacted]	[redacted]
Δ BASMI	**TOF**	[redacted]	[redacted]
Δ ASQoL[b]	**TOF**	[redacted]	[redacted]
Δ SF36 PCS	**TOF**	[redacted]	[redacted]
Δ SF36 MCS	**TOF**	[redacted]	[redacted]

Underlined value indicates where tofacitnib is superior to the alternative treatment
Abbreviations: TOF- tofacitinib, ADA- adalimumab, PBO- placebo
a, unless otherwise indicated. b. unadjusted fixed model outcomes are presented, since RE model comparison was not conducted due to few number of studies

Network diagrams, model fit statistics and heterogenicity statistics as well as response rates by study and study arm for each presented outcome are presented in **Appendix D**. No statistically significant results were observed for tofacitinib vs adalimumab. Each network by outcome is described in brief detail below.

ASAS20 Response

A total of six studies were included in the network for ASAS20. There [redacted] in ASAS20 response between tofacitinib and adalimumab in both mixed and naïve populations.

ASAS40 Response

A total of six studies were included in the network for ASAS40. There [redacted] in achieving ASAS40 response between tofacitinib and adalimumab in both mixed and naïve populations.

BASDAI50 Response

A total of four studies were included in the network for BASDAI50. There [redacted] in achieving BASDAI50 response between tofacitinib and adalimumab in both mixed and naïve populations.

BASDAI change from baseline (continuous outcome)

A total of six studies were included in the network for BASDAI. There was [redacted] in the BASDAI decrease between tofacitinib and adalimumab in both mixed and naïve populations.

BASFI change from baseline (continuous outcome)

A total of five studies were included in the network for BASFI. There was [redacted] in the BASFI decrease between tofacitinib and adalimumab in both mixed and naïve populations.

BASMI change from baseline (continuous outcome)

A total of five studies were included in the network for BASMI. There was [redacted] in the BASMI decrease between tofacitinib and adalimumab in both mixed and naïve populations.

ASQoL change from baseline (continuous outcome)

A total of three studies were included in the network for ASQoL. RE model analysis was not conducted due to high levels of convergence as a result of there being too few data points to properly estimate the number of parameters. Using a FE model for comparison, there [redacted] in the ASQoL decrease between tofacitinib and adalimumab in both mixed and naïve populations.

SF-36v2 change from baseline (continuous outcome)

A total of five and four studies were included in the network for SF-36v2 PCS and SF-36v2 MCS respectively. There was [redacted] for outcomes between tofacitinib and adalimumab in mixed and naïve populations with regards to either scale.

A summary of pairwise results for conducted analyses is provided in **Table 22**.

Table 22: NMA Outcomes- Random Effects without Baseline Risk Adjustment[a]

	Mixed population			Treatment-Naïve Population		
	TOF vs PBO	**ADA vs PBO**	**TOF vs ADA**	**TOF vs PBO**	**ADA vs PBO**	**TOF vs ADA**
ASAS20 OR (95% CI)						
ASAS40 OR (95% CI)						
BASDAI50 OR (95% CI)						
Δ BASDAI Mean difference (95% CI)						
Δ BASFI Mean difference (95% CI)						
Δ BASMI Mean difference (95% CI)						
Δ ASQoL[b] Mean difference (95% CI)						
Δ SF-36v2 PCS Mean difference (95% CI)						

Δ SF-36v2 MCS Mean difference (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a, unless otherwise indicated. b. unadjusted fixed model outcomes are presented, since RE modela. comparison was not conducted due to few number of studies

Odds ratio outlined in **bold** indicates significant outcomes.

Justification for Random Effects Model

Bayesian models for both FE and RE models were conducted for all networks. Results presented in Document B are RE outcomes without baseline risk adjustment. These results were presented for various reasons:

- Substantial heterogeneity was observed for many outcomes (defined as an I^2 value above 50%); outcomes and drivers of heterogeneity are described in **Appendix D**
- The DIC and total residual deviance were calculated for all FE and RE networks where possible and these are presented in **Appendix D**. The DIC was comparable between the various models and under those circumstances, the RE model was selected, as it has previously been recommended for interpreting outcomes of NMAs with fewer than 10 studies.

Overall summary of NMA evidence

Multiple tofacitinib and adalimumab trials populated each network. All adalimumab trials previously included in TA383 and TA407 were included in this NMA, with the exception of one study that was excluded from the core NMA outcomes presented in Document B. This trial (Hu et al. 2012) was regarded to have significant bias due to concerns with deviations from intended interventions (blinding), random sequence generation, allocation concealment, and a high risk of bias due to the selection of reported results (see **Appendix D**). There was also one study that was identified in addition to the adalimumab studies included in TA383 and TA407 (COAST-V).

No statistically significant differences were observed between tofacitinib and adalimumab across all efficacy and HRQoL outcomes, in mixed and treatment naïve populations. No outcomes from the RE NMA with unadjusted baseline risk could be reported for ASQoL as few studies were identified, causing high levels of convergence, therefore in that case FE unadjusted baseline risk outcomes for tofacitinib vs adalimumab were presented.

Uncertainties in the indirect and mixed treatment comparisons

Heterogeneity was observed between trials for adalimumab vs placebo in the following outcomes: ASAS20 ([redacted]), ASAS40 ([redacted]), BASDAI50 ([redacted]), and SF-36v2 PCS ([redacted]). Heterogeneity was also observed for tofacitinib vs placebo in BASMI outcomes ([redacted]). Drivers of heterogeneity are described in **Appendix D**.

B.3.10 Adverse reactions

Manageable safety and tolerability profile

- **Tofacitinib has a comparable safety profile (as shown by results for overall discontinuations, AE related discontinuations and serious infections) compared to other bDMARDs when evaluating safety during the randomised, placebo-controlled trial period.**
- **No new potential safety risks were identified for AS patients treated with tofacitinib**
- **The proportion of patients who experienced all-causality TEAEs was slightly higher in the tofacitinib 5 mg BID group compared to placebo up to Week 16 and placebo advanced to tofacitinib 5 mg BID up to Week 48**
- **Through to week 48, the majority of adverse events with tofacitinib were mild or moderate**
- **Patients treated with tofacitinib experienced no new occurrences or flares of IBD or other common extra-articular manifestations of AS during treatment**

Discontinuations and withdrawals

- **The proportion of patients who discontinued study drug due to AEs was low**
- **There was a slightly higher proportion of patients receiving tofacitinib 5 mg BID in the A3921120 trial that temporarily or permanently discontinued study drug due to AEs compared with placebo up to Week 16 and compared with patients who advanced to tofacitinib 5 mg BID after placebo up to Week 48**

- **There were no adverse events that lead to permanent discontinuation in more than one patient**

Risks

- **The system organ classes with the highest incidence included infections and infestations and gastrointestinal disorders**
- **No opportunistic infections were recorded in the A3921119 and A3921120 trials**
- **No adjudicated malignancies, cardiovascular events/ nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death, interstitial lung disease, gastrointestinal perforations, or pulmonary embolisms/ deep vein thromboses/ arterial thromboembolisms were reported in either study**

Deaths

- **No deaths were recorded in the A3921119 and A3921120 trials**

Comparative safety

- **Tofacitinib has a comparable safety profile to adalimumab when evaluating safety during the randomised, placebo-controlled period in an AS population.**

In this section, tofacitinib safety outcomes reported in Phase 2 and Phase 3 trials at 5 mg BID are reviewed.

A summary of pooled data from both trials for the Tofacitinib licenced dose (5 mg BID) regarding TEAEs occurring in ≥2%, AEs Leading to Discontinuation Serious Adverse Events and Serious Infections is provided in the **Appendix I.**

Overview of AEs in the Phase 2 A3921119 (NCT01786668) trial

In the A3921119 trial, the proportion of patients who experienced TEAEs was slightly higher in the tofacitinib 5 mg BID (28 [53.8%] patients) treatment group compared to placebo (22 [43.1%] patients). The proportion of patients who experienced SAEs was highest in the placebo treatment group (3.9%). A small proportion of patients

experienced severe TEAEs: one (1.9%) subject in the tofacitinib 5 mg BID treatment group and three (5.9%) patients in the placebo treatment group (50, 56).

The proportion of patients with SAEs and TEAEs leading to discontinuation was low. Overall, one (1.9%) subject in the tofacitinib 5 mg BID treatment group and three (5.9%) patients in the placebo treatment group discontinued the study due to a TEAE. These TEAEs included peripheral swelling (tofacitinib 5 mg BID treatment group) and spinal pain, hypertransaminasemia, and pregnancy (placebo treatment group); all TEAEs other than pregnancy were considered by the investigator to be related to the study drug. A small proportion of patients experienced TEAEs that led to dose reductions or temporary discontinuations. There were no deaths in the study (50, 56). Table 23 summarises the all-causality TEAEs in A3921119.

Table 23: Treatment-Emergent Adverse Events (All Causalities) – Study A3921119

	Tofacitinib 5mg BID n (%)	**Placebo n (%)**
Patients evaluable for adverse events	52	51
Number of adverse events	[redacted]	[redacted]
Patients with adverse events	28 (53.8)	22 (43.1)
Patients with serious adverse events	1 (1.9)	2 (3.9)
Patients with severe adverse events	[redacted]	[redacted]
Patients discontinued due to adverse events	1 (1.9)	3 (5.9)
Patients with dose reduced or temporary discontinuation due to adverse events	[redacted]	[redacted]

Source: (Pfizer data on file 2017, van der Heijde 2017)

Abbreviations: BID= Twice daily; MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients in each adverse event category, TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of patients in the Safety Analysis Set.

Includes data up to 999 days after last dose of study drug.

An adverse event is considered to be a treatment-emergent adverse event (TEAE) if the onset is after the start of the first dose of study treatment through the last subject visit, or the onset is prior to the first dose of study treatment and worsens in severity after the first dose of study treatment through the last subject visit. Except for the Number of Adverse Events row, patients are counted only once per treatment in each row. For the Number of Adverse Events row, patients are counted once per treatment and preferred term. MedDRA (v18.0) coding dictionary applied.

In all treatment groups, the most frequently experienced TEAEs were in the system organ class of infections and infestations. [redacted] and [redacted] patients experienced at least one infection and/or infestation in the tofacitinib 5mg BID and placebo treatment groups respectively (56). Overall, the most frequently experienced TEAEs by preferred term were:

- Nasopharyngitis [redacted], ALT increased [redacted], blood creatine phosphokinase increased [redacted], arthralgia [redacted], and headache [redacted] in the tofacitinib 5 mg BID treatment group.
- Nasopharyngitis [redacted], bronchitis [redacted], dizziness [redacted], and rash [redacted] in the placebo treatment group.

Overall, the most frequently experienced TEAEs by preferred term were nasopharyngitis (tofacitinib 5 mg BID, and placebo treatment groups) and upper respiratory tract infection (tofacitinib 2 mg BID and tofacitinib 10 mg BID treatment groups) (50, 56). **Table 23Table 24** summarises the incidence of all-causality TEAEs by system organ class in >2 patients in any treatment group in A3921119 (50, 56).

Table 24: Incidence of Treatment-Emergent Adverse Events (All Causalities) by System Organ Class in ≥2 Patients in Any Treatment Group – Study A3921119

	Tofacitinib 5mg BID n (%)	**Placebo n (%)**
Evaluable for adverse events	52	51
With adverse events	28 (53.8)	22 (43.1)
Discontinued due to adverse events	1 (1.9)	3 (5.9)
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]

	Tofacitinib 5mg BID n (%)	Placebo n (%)
Bronchitis	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]
Ligament sprain	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]

Source: (56)

Abbreviations: BID= Twice daily; MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients in each adverse event category, TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of patients in the Safety Analysis Set.

An adverse event is considered to be a treatment-emergent adverse event (TEAE) if the onset is after the start of the first dose of study treatment through the last subject visit, or the onset is prior to the first dose of study treatment and worsens in severity after the first dose of study treatment through the last subject visit. MedDRA (v18.0) coding dictionary applied.

Overview of AEs in the Phase 3 A3921120 (NCT03502616) trial

In the A3921120 trial, the safety profile of tofacitinib showed that the proportion of patients who experienced all-causality TEAEs was slightly higher in the tofacitinib 5 mg BID group compared to placebo up to Week 16 and placebo advanced to tofacitinib 5 mg BID up to Week 48. The majority of reported all-causality TEAEs were mild to moderate in both treatment groups up to Weeks 16 and 48; with a low number of severe TEAEs occurring in the tofacitinib 5 mg BID group. All SAEs up to Weeks 16

and 48 were in patients who received tofacitinib 5 mg BID ([redacted]).

Up to Weeks 16 and 48, a higher proportion of patients in the tofacitinib 5 mg group discontinued study drug or had a temporary discontinuation due to AEs ([redacted]). There were no deaths in the study (51, 57). **Table 25** summarises the all-causality TEAEs in A3921120.

Table 25: Treatment-Emergent Adverse Events (All Causalities) – A3921120

	16-weeks		48-weeks	
	Tofacitinib 5mg BID n (%)	**Placebo n (%)**	**Tofacitinib 5mg BID n (%)**	**Placebo → Tofacitinib 5mg BID n (%)**
Patients evaluable for adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Number of adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Patients with adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Patients with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Patients with severe adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Patients discontinued study drug due to adverse events (a)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose reduced or temporary discontinuation due to adverse events	[redacted]	[redacted]	[redacted]	[redacted]

Source: (51, 57)

Abbreviations: BID= Twice daily

For Up to Week 16, included all data collected since the first dose of investigational product and up to week 16 (including week 16). For Up to Week 48, included all data collected since the first dose of investigational product and up to the end of study including follow-up.

Except for the Number of Adverse Events, patients were counted only once per treatment in each row.

Serious Adverse Events - according to the investigator's assessment.

(a) Patients who had an AE record that indicated that Action Taken with Study Treatment was Drug Withdrawn
MedDRA v22.1 coding dictionary applied.

The most commonly reported all-causality TEAEs (>10% of patients) in all treatment groups were gastrointestinal disorders, infections and infestations, investigations (in the placebo advanced to tofacitinib 5 mg BID group up to Week 48 only), and musculoskeletal and connective tissue disorders (51, 57). The most common all-causality TEAEs (≥2% of patients) reported up to Weeks 16 and 48 included:

- In the tofacitinib 5mg group: Upper respiratory tract infection, nasopharyngitis, and diarrhoea

- In the placebo and placebo advanced to tofacitinib 5mg BID groups: Upper respiratory tract infection, nasopharyngitis, and arthralgia (51, 57).

At Weeks 16 and 48, there was a slightly higher incidence of Upper respiratory tract infections among patients receiving tofacitinib 5mg BID from baseline. The incidence of Viral respiratory tract infections was also slightly higher among patients (51, 57). Non-serious infection events included the following:

- Up to Week 48 in the tofacitinib 5 mg BID AEs included: non-serious herpes ophthalmic ([redacted]), non-serious herpes zoster ([redacted]), and meningitis ([redacted]). The case of herpes ophthalmic did not meet opportunistic infection criteria.

- Up to Week 48 in the placebo advanced to tofacitinib 5 mg BID group [redacted] reported non-serious herpes zoster (51, 57).

Table 26 summarises the incidence of all-causality TEAEs in A3921120

Table 26: Incidence of Treatment-Emergent Adverse Events (All Causalities) by Preferred Term in ≥2% of Patients in Any Treatment Group – A3921120

Number (%) of Patients: by preferred term	16-weeks			48-weeks		
	Placebo (N=136) n (%)	**Placebo (N=136)** n (%)	**Relative risk (95% CI)**	**Tofacitinib 5mg BID (N=133)** n (%)	**Placebo → Tofacitinib 5mg BID (N=136)** n (%)	**Relative risk (95% CI)**
Upper respiratory tract infection	14 (10.5)	10 (7.4)	[redacted]	21 (15.8)	18 (13.2)	[redacted]
Nasopharyngitis	9 (6.8)	10 (7.4)	[redacted]	11 (8.3)	17 (12.5)	[redacted]
Diarrhoea	6 (4.5)	5 (3.7)	[redacted]	10 (7.5)	8 (5.9)	[redacted]
Alanine aminotransferase increased	4 (3.0)	1 (0.7)	[redacted]	8 (6.0)	2 (1.5)	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Headache	2 (1.5)	3 (2.2)		5 (3.8)	7 (5.1)	[redacted]
Hepatic function abnormal	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

Number (%) of Patients: by preferred term	16-weeks			48-weeks		
	Placebo (N=136) **n (%)**	**Placebo (N=136)** **n (%)**	**Relative risk (95% CI)**	**Tofacitinib 5mg BID (N=133)** **n (%)**	**Placebo → Tofacitinib 5mg BID (N=136)** **n (%)**	**Relative risk (95% CI)**
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein urine present	4 (3.0)	2 (1.5)	[redacted]	5 (3.8)	4 (2.9)	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Respiratory tract infection viral	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Blood alkaline phosphokinase increased	[redacted]	[redacted]		[redacted]	[redacted]	
Blood creatine phosphokinase increased	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]		[redacted]	[redacted]	
Blood pressure increased	[redacted]	[redacted]		[redacted]	[redacted]	

Number (%) of Patients: by preferred term	16-weeks			48-weeks		
	Placebo (N=136) **n (%)**	**Placebo (N=136)** **n (%)**	**Relative risk (95% CI)**	**Tofacitinib 5mg BID (N=133)** **n (%)**	**Placebo → Tofacitinib 5mg BID (N=136)** **n (%)**	**Relative risk (95% CI)**
Cholelithiasis	[redacted]	[redacted]		[redacted]	[redacted]	
Dyspepsia	[redacted]	[redacted]		[redacted]	[redacted]	
Gastrooesophageal reflux disease	[redacted]	[redacted]		[redacted]	[redacted]	
Haematuria	[redacted]	[redacted]		[redacted]	[redacted]	
Herpes zoster	[redacted]	[redacted]		[redacted]	[redacted]	
Latent tuberculosis	[redacted]	[redacted]		[redacted]	[redacted]	
Lipids increased	[redacted]	[redacted]		[redacted]	[redacted]	
Oral herpes	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Abdominal pain upper	0	4 (2.9)	[redacted]	2 (1.5)	7 (5.1)	[redacted]
Arthralgia	1 (0.8)	9 (6.6)	[redacted]	2 (1.5)	9 (6.6)	[redacted]
Cough	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]		[redacted]	[redacted]	

Number (%) of Patients: by preferred term	16-weeks			48-weeks		
	Placebo (N=136) n (%)	Placebo (N=136) n (%)	Relative risk (95% CI)	Tofacitinib 5mg BID (N=133) n (%)	Placebo → Tofacitinib 5mg BID (N=136) n (%)	Relative risk (95% CI)
Pharyngitis	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Tonsilitis	[redacted]	[redacted]		[redacted]	[redacted]	
Toothache	[redacted]	[redacted]		[redacted]	[redacted]	
Urinary tract infection	[redacted]	[redacted]		[redacted]	[redacted]	
Abdominal discomfort	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]		[redacted]	[redacted]	
Joint swelling	[redacted]	[redacted]		[redacted]	[redacted]	
Spinal pain	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]		[redacted]	[redacted]	
Uveitis	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

Source: (51, 57).

Abbreviations: BID= Twice daily; Inf= Infinite

Patients were counted only once per treatment per event. Any adverse events with >= 2% of patients in any treatment group were counted in this table. MedDRA v22.1 coding dictionary applied. Adverse events are shown by descending frequency on Tofacitinib 5 mg BID under Up to Week 48 column.

Comparable Safety and adverse events

The full methodology of the SLR conducted to inform the NMA is described in **Appendix D**. The same six RCTs identified for the NMA of clinical effectiveness outcomes were retained for the NMA of safety and adverse events. As described above, the Hu et al. 2012 publication was omitted from the NMA of safety and adverse events due to bias. A listing of articles included in the SLR and those that were included and excluded in the NMA along with the rationale is provided in **Appendix D.** Due to the lack of availability on safety data according to bDMARD/TNFi exposure subgroup, the safety NMAs were conducted for the entire study sample, irrespective of bDMARD/TNFi exposure. The following safety and adverse event outcomes were reviewed in the SLR and considered for the NMA:

- Overall discontinuation
- Adverse Event Related Discontinuation
- Serious Adverse events

Results for only one of these outcomes (discontinuations) could be assessed in the NMA.

Discontinuations

A total of five studies were included in the network for all discontinuation events. There [redacted] in discontinuations between tofacitinib and adalimumab in the mixed population (**Table 27**). Moderate heterogeneity was observed for tofacitinib vs. placebo, with higher rates of discontinuation for placebo observed in A3921119 compared to A3921120 (7.8% vs. 2.9%) and higher rates of discontinuation for tofacitinib arms for A3921120 compared to A3921119 (3.8% and 1.9%). It was unclear what was driving this difference.

Table 27: Random Effects without Baseline Risk Adjustment for Discontinuation Events

	Mixed Population, OR (95% CrI)
Tofacitinib vs Placebo	[redacted]
Adalimumab vs Placebo	[redacted]
Tofacitinib vs Adalimumab	[redacted]

Abbreviations: CrI: Credible interval; OR: Odds ratio

Discontinuations due to AEs

A total of five studies were identified for inclusion in the network of discontinuations due to AEs. Because all adalimumab comparisons had a zero-event placebo arm, no NMA was performed. A descriptive summary of discontinuations due to AEs can be found in **Appendix F**.

Serious Adverse Events

A total of five studies were also identified for inclusion in the network of serious adverse events. No NMA was conducted as there were significant issues with autocorrelation when adjusting for baseline risk. A descriptive summary of serious adverse events can be found in **Appendix F**.

Opportunistic Infections

There was limited reporting of opportunistic infections in the literature. Among studies where reporting of opportunistic infections was available, [redacted] were observed in any of the studies during the placebo-controlled period.

Herpes Zoster

The inclusion of herpes zoster or tuberculosis was not consistently reported between studies and therefore we could not meaningfully compare opportunistic infections with and without this condition between studies. [redacted] of herpes zoster were observed for tofacitinib 5 mg in Studies A3921119 and A3921120 during the placebo-controlled period.

Malignancy (Excluding NMSC)

Malignancy was seldomly observed in the literature during the placebo-controlled periods. No cases of malignancy were observed from tofacitinib 5 mg within A3921119 and A3921120. Where malignancy was specifically mentioned, no cases of malignancy were reported in the treatment arms for the remaining studies.

B.3.13 Conclusions about comparable health benefits and safety

Treatment choice is largely driven by informed discussion and consensus between the prescribing clinician and the patient, based on the level of disease activity, patient risk tolerance, patient preference, and patient lifestyle considerations. Tofacitinib will provide an alternative treatment option for people with active AS for whom NSAIDs, have been inadequately effective or not tolerated. As an oral JAK inhibitor indicated for AS, tofacitinib provides a safe and effective alternative route of administration that eliminates the physical and psychological patient burden of injections.

In both the A3921119 and A3921120 trials, tofacitinib demonstrated AS-related signs and symptoms alleviation by showing significantly greater ASAS20, ASAS40 and BASDAI50 response rates compared with placebo at Week 12 and Week 16. In A3291120, tofacitinib showed rapid efficacy onset, confirmed by a significant reduction in disease activity compared with placebo, and significant alleviation of back pain in as early as two weeks. Efficacy and improvements in HRQoL were demonstrated in up to 48-weeks follow-up. Tofacitinib was also consistently efficacious across subgroups of prior treatment history (bDMARD naïve and TNFi-IR or bDMARD use [Non-IR]), as assessed by ASAS20 and ASAS40 response rates.

The NMA described in this submission incorporates the key clinical outcomes and outcomes used in the cost effectiveness models of past HTAs (TA383, TA407 and TA718; see Section B2). This NMA showed that there [redacted] tofacitinib and adalimumab across all efficacy and HRQoL outcomes in mixed and treatment naïve populations. Therefore, tofacitinib can be considered [redacted] with respect to these outcomes in the treatment of AS.

Tofacitinib has an established safety profile in other indications and during the A3921119 and A3921120, no new safety signals or issues related to treatment of AS patients with tofacitinib were detected. Due to the lack of data availability on safety data according to bDMARD/TNFi exposure subgroup, safety NMAs were conducted for the entire study samples. The NMA demonstrated that there

[redacted] between tofacitinib and adalimumab.

B.4 Cost- comparison analysis

NMA results have demonstrated that Tofacitinib 5mg BID has similar efficacy, safety and QoL outcomes to adalimumab. Therefore, costs included in the cost comparison are limited to:

- Drug acquisition costs
- Administration costs
- Monitoring costs

B.4.1 Changes in service provision and management

As an oral treatment, tofacitinib is expected to be associated with reduced administration costs compared to adalimumab which is administered subcutaneously. Monitoring requirements are anticipated to be comparable. Treatment will be provided in a secondary care setting.

Administration

Tofacitinib is the first orally administered treatment, that will be available for patients with AS. All currently available biological treatment options are administered parenterally, either as SC injection or IV formulation.

It is expected that tofacitinib will be associated with modest cost savings in terms of administration costs versus adalimumab, which is administered subcutaneously. As an oral treatment, tofacitinib is assumed to be associated with no administration costs.

For SC administration of adalimumab, it is assumed that patients would self-administer following one-off training by a nurse in a GP practice. This is in line with assumptions made and accepted in TA383 (1). The cost of training is assumed to be £42 which corresponds with one hour of nurse time from PSSRU Unit Costs of Health and Social Care 2020 (Nurse - GP practice. Cost per hour including qualifications) (61).

Monitoring

The monitoring costs included in the cost comparison analysis are informed by the resource use applied in NICE TA383. Sources for the unit costs associated with on-

treatment monitoring were taken from the ixekizumab appraisal (3) with costs updated to the latest public prices. Compared with adalimumab, tofacitinib is associated with additional monitoring in the form of assessment of lipid parameters. In line with the summary of product characteristics for tofacitinib, assessment of lipid parameters should be performed after eight weeks following initiation of tofacitinib therapy. To account for lipid parameters testing in the cost comparison analysis, tofacitinib is associated with one additional haematology test (£2.58), (currency code DAPS05 – directly accessed pathology services, haematology) (62). Full details are provided in Section B.4.3.3.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Overview of analysis inputs and assumptions

A simple cost comparison was developed to evaluate the cost to the NHS of treating patients with active ankylosing spondylitis with tofacitinib compared adalimumab. The NMA of efficacy and safety has demonstrated that tofacitinib provides similar health benefits to adalimumab. As such, the cost comparison analysis focuses on drug acquisition, drug administration and drug monitoring costs and presents results for the first year and for subsequent years separately, to reflect the training requirements for SC administration for adalimumab in the first year. Only direct medical costs were included in the model. Adverse event costs were excluded considering the comparable safety profile for tofacitinib and adalimumab. Similarly, disease management costs were excluded given the comparable efficacy outcomes on BASDAI and BASFI measures in the network meta-analysis. Discounting of costs was not considered.

B.4.2.2 Features of the cost-comparison analysis

Costs are assessed for the first year of treatment and separately for subsequent years to take account of differing administration requirements during the induction phase of adalimumab treatment and the requirement for assessment of lipid parameters after eight weeks following initiation of tofacitinib treatment. Costs are not discounted. This is in line with the user guide for cost comparison for fast-track appraisal.

No treatment effects are included in the model, with the analysis focused on comparing drug acquisition, drug administration and drug monitoring costs. Treatment discontinuation was not included since the NMA concluded that there was no

statistically significant difference in all-cause discontinuations between tofacitinib and adalimumab in the mixed population (**Table 27**). Further, adverse events were not included since tofacitinib has a comparable safety profile to adalimumab when evaluating safety during the randomized, placebo-controlled period in an AS population (see Section B.3.10). It is therefore assumed in the analysis that patients stay on treatment throughout the entire year in which they started treatment.

Mortality is also not considered within the analysis; this is not expected to differ between tofacitinib and adalimumab.

Unit costs for drug acquisition were sourced from the British National Formulary (BNF 2021) using the lowest biosimilar cost for adalimumab. Unit costs for drug administration for subcutaneous therapies were sourced from the Personal Social Services Research Unit (PSSRU 2020) using the cost per hour of a nurse in a GP practice including qualifications (61). Unit costs for monitoring were also sourced from National Schedule of NHS Costs 2019-2020 (62) and the Technology Assessment Report for TA199 (63) in line with the assumptions made in NICE TA718 (3), with costs updated to the current price year. The monitoring resource use were sourced from NICE TA383, consistent with assumptions also made in other appraisals (4).

B.4.2.3 Intervention and comparators' acquisition costs

Drug acquisition costs for tofacitinib and for adalimumab are summarised in Table 28. Treatment posology was taken from the Summary of Product Characteristics (SmPC) for each product with drug acquisition costs sourced from the British National Formulary (BNF 2021) using the lowest biosimilar cost for adalimumab. Tofacitinib is provided to the NHS at a [redacted].

Table 28: Acquisition costs of the intervention and comparator technologies

Treatment	Tofacitinib	Adalimumab biosimilar
Brand name	Xeljanz	Amgevita
Pharmaceutical formulation	5 mg film-coated tablets	40 mg solution for injection in pre-filled pen or syringe
Acquisition cost (list price, excluding VAT)	£690.03 (pack of 56)	£633.60 (pack of 2)

Method of administration	Oral	Subcutaneous injection
Doses and frequency	5mg twice daily	40mg Q2W
Annual cost assumption	Assuming 365 days in a year	
Annual drug acquisition costs	£8,995 [redacted]	£8,259

Abbreviations: mg: milligram; Q2W: every two weeks; VAT: value-added tax.

B.4.2.4 Intervention and comparators' healthcare resource use and associated costs

Administration costs

As an oral treatment, tofacitinib is assumed to be associated with no administration costs.

For SC administration of adalimumab, it is assumed that patients would self-administer following one-off training by a nurse in a GP practice. This is in line with assumptions made and accepted in TA383 (1). The cost of this training is assumed to be £42 which corresponds to one hour of nurse time from PSSRU Unit Costs of Health and Social Care 2020 (Nurse - GP practice. Cost per hour including qualifications) (61). Unit costs for administration are presented in Table 29.

Table 29: Unit costs for administration

	Unit cost	Source
Administration cost oral therapies	£0.00	No cost assumed for oral treatments
Administration cost for SC therapies	£42.00	PSSRU Unit Costs of Health and Social Care 2020. Cost per hour of nurse time, including qualifications (GP practice). (61)

Abbreviations: GP: general practitioner; PSSRU: Personal Social Services Research Unit; SC: subcutaneous.

Annual administration costs for tofacitinib and adalimumab are presented in Table 30.

Table 30: Drug administration costs of the intervention and comparator technologies

Treatment	Tofacitinib	Adalimumab biosimilar
Administration assumptions	No administration costs (oral therapy)	One-off training for self-administration in year 1

Drug administration costs in year 1	£0.00	£42.00
Drug administration costs in subsequent years	£0.00	£0.00

Monitoring costs

The monitoring resource use included in the cost comparison analysis is informed by the resource use applied in TA383 and reflects the summary of product characteristics for the individual treatments (1). The resource use numbers are also aligned with the assumptions made for adalimumab in TA407 and TA718 (3, 4). Tofacitinib is assumed to be associated with additional monitoring in the form of assessment of lipid parameters. In line with the summary of product characteristics for tofacitinib, assessment of lipid parameters should be performed after 8 weeks following initiation of tofacitinib therapy.

Sources for the unit costs associated with on-treatment monitoring were taken from the ixekizumab appraisal TA718 (3). The ixekizumab appraisal referenced the National Schedule of NHS Costs for 2017-18 for most items, except for a tuberculosis test. For this item, the cost was inflated from the Technology Assessment Report for TA199 (63). The National Schedule of NHS Costs for 2019-2020 was used to provide the latest public price for the remaining laboratory tests and for a specialist visit. (62)

We note that other previous appraisals, namely TA383 and TA407, have inflated costs presented in TA199. Since TA199 itself reported inflation of costs from 2005, inflating these costs to 2019/2020 using the latest HCHS/NHSCII pay and prices inflation index in PSSRU Unit Costs of Health and Social Care was not believed to be the most accurate approach. We therefore chose to use, and update cost sources presented and accepted in the recent NICE submission for ixekizumab (TA718). We also note the minimal impact of the choice of approach since tofacitinib and adalimumab are assumed to be associated with the same monitoring requirements, with the exception of the assessment of lipid parameters after 8 weeks for patients receiving tofacitinib.

The cost of a haematology test from directly accessed pathology services is assumed for the assessment of lipid parameters for tofacitinib patients, using the cost reported in the National Schedule of NHS Costs for 2019-2020. (62)

Unit costs for monitoring are presented in Table 31.

Table 31: Unit costs for monitoring

Item	Unit cost	Source
Full blood count	£2.58	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology). (62)
Erythrocyte sedimentation rate	£2.58	
Liver function test	£1.22	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS04 – clinical biochemistry). (62)
Urea and electrolytes	£1.22	
Chest X-Ray	£32.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Direct access plain film (Currency code DAPF). (62)
Tuberculosis test	£9.47	Rodgers et al. (2011) cost (£8.01) inflated to 2019/20 prices based on the HCHS/NHSCII pay and prices inflation index in PSSRU Unit Costs of Health and Social Care 2020. (63) (61)
Antinuclear antibody	£2.58	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology). (62)
Double-stranded DNA test	£2.58	
Specialist visit	£155.06	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Consultant-led non-admitted face-to-face attendance, follow-up. (Currency code WF01A). (62)
Lipid parameters	£2.58	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology). (62)

Abbreviations: DNA: deoxyribonucleic acid; HCHS: hospital & community health services; NHS: National Health Service; NHSCII: NHS cost inflation index; PSSRU: Personal Social Services Research Unit.

Monitoring requirements and costs for tofacitinib and adalimumab are presented in Table 32 and Table 33 for the initiation period (first 12 weeks) and for ongoing quarterly monitoring, respectively.

Table 32: Drug monitoring during initiation period (first 12 weeks of treatment)

	Resource use	
	Tofacitinib	**Adalimumab**
Full blood count	2	2
Erythrocyte sedimentation rate	2	2

Liver function test	2	2
Urea and electrolytes	2	2
Chest X-Ray	1	1
Tuberculosis test	1	1
Antinuclear antibody	1	1
Double-stranded DNA test	1	1
Specialist visit	2	2
Lipid parameters	1	0
Total cost for first 12 weeks	**£375.03**	**£372.46**

Abbreviations: DNA: deoxyribonucleic acid

Table 33: Drug monitoring during ongoing quarterly monitoring (following initial 12 weeks)

	Resource use	
Treatment	**Tofacitinib**	**Adalimumab**
Full blood count	1	1
Erythrocyte sedimentation rate	1	1
Liver function test	1	1
Urea and electrolytes	1	1
Chest X-Ray	0	0
Tuberculosis test	0	0
Antinuclear antibody	0	0
Double-stranded DNA test	0	0
Specialist visit	0.5	0.5
Lipid parameters	0	0
Total cost for subsequent quarters	**£85.12**	**£85.12**

Abbreviations: DNA: deoxyribonucleic acid

B.4.3.4 Adverse reaction unit costs and resource use

Adverse reactions were not included in the cost comparison analysis due to the comparable safety profile of tofacitinib and adalimumab.

B.3.4.5 Miscellaneous unit costs and resource use

Further costs and resource use were not included in the cost comparison analysis.

B.3.4.6 Clinical expert validation

Clinical expert validation was not sought for the cost and healthcare resource use values as this information was taken from the most recent NICE appraisals in this therapy area.

B.4.3 Base-case results

Base case results for the cost comparison analysis are presented in Table 34 for the initiation year and in Table 35 for subsequent years.

At list price, tofacitinib has a higher but broadly similar cost to adalimumab (total cost of £9,632 for tofacitinib versus £8,935 for adalimumab in year, and total cost of £9,342 for tofacitinib versus £8,606 for adalimumab in subsequent years).

At the discounted PAS price for tofacitinib, tofacitinib is associated with cost savings versus adalimumab (total cost of [redacted] for tofacitinib versus £8,935 for adalimumab in year one, and total cost of [redacted] for tofacitinib versus £8,606 for adalimumab in subsequent years).

Table 34: Base case results – initiation year

Treatment	Tofacitinib	Adalimumab biosimilar
Acquisition cost	£8,995 [redacted]	£8,259
Administration cost	£0	£42
Monitoring cost	£630	£628
Total cost	**£9,625** [redacted]	**£8,929**
Difference versus tofacitinib (list price)	-	**£691**
[redacted]	-	[redacted]

Table 35: Base case results – subsequent years

Treatment	Tofacitinib	Adalimumab biosimilar
Acquisition cost	£8995 [redacted]	£8,259
Administration cost	£0	£0
Monitoring cost	£340	£340
Total cost	**£9,336** [redacted]	**£8,600**
Difference versus tofacitinib (list price)	-	**£730**
[redacted]	-	[redacted]

B.4.4 Sensitivity and scenario analyses

No sensitivity or scenario analyses were considered.

B.4.5 Subgroup analysis

No sub-group analysis was considered. Drug acquisition, drug administration and drug monitoring costs are not expected to be different for tofacitinib and adalimumab in biologic-naïve and biologic-experienced patients. The modest cost savings associated with tofacitinib administration versus adalimumab may not be realised in a biologic-experienced patient population previously treated and trained on how to self-administer a SC therapy.

B.4.6 Interpretation and conclusions of economic evidence

In summary, at its discounted PAS price, tofacitinib represents a [redacted] for the NHS in England compared with adalimumab, supporting its reimbursement as a valuable treatment alternative for patients with active AS.

[redacted] is believed to be relevant to all patients identified in the

decision problem, namely people with radiographic ankylosing spondylitis for whom nonsteroidal anti-inflammatory drugs have been inadequately effective or not tolerated. Further, [redacted] the analysis is highly relevant and generalisable to clinical practice in England.

The analysis has focused on drug acquisition costs, drug administration costs and drug monitoring costs since it is anticipated that adverse event and disease management costs would be comparable between treatments, in line with the results of the NMA. As such, the analysis has focused on the key areas of difference between the two treatments, providing transparent and easily interpretable results. The analysis has been informed by previous NICE appraisals and is based on the latest publicly available national sources for drug acquisition, administration and monitoring costs.

A limitation of the analysis is the unavailability of confidential price discount information for adalimumab biosimilar.

B.5 References

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B.6 Appendices

Appendix C: Summary of product characteristics or information for use
Appendix D: Identification, selection and synthesis of clinical evidence
Appendix E: Post-hoc Subgroup analysis
Appendix F: Adverse reactions
Appendix G: Published cost-effectiveness studies
Appendix H: Confidential information checklist
Appendix I: Additional outcomes from A3921119 and A3921120

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tofacitinib for treating active ankylosing spondylitis ID3865

Clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID3865 Tofacitinib for AS ERG Clarification questions Pfizer comments [CIC]	V0.1	Yes	21.01.2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Questions on the systematic literature review

A1. The only clinical evidence searches documented were conducted on 5th August 2019. The update searches (from April 2021) were not included in the main company submission (Document B). Please can the update searches be provided and documented fully with the exact date of the search, strategies, hits per line, and an updated PRISMA diagram.

The search was updated on 11 April 2021 and no new studies were identified. Please see an updated table on MEDLINE/Embase (ProQuest) Search Strings (as of April 2021) below (Table 1). The PRISMA diagram presented in Figure 1 in Appendix D.1.2 is correct and contains the number of studies as of April 2021.

Table 1: MEDLINE/Embase (ProQuest) Search Strings (as of April 2021)

Topic	Set	String	Results
Ankylosing spondylitis	S1	TI,AB(Ankylosing spondylitis) OR EMB.EXACT("ankylosing spondylitis") OR MESH.EXACT("Spondylitis, Ankylosing") OR (TI,AB("axial spondyloarthritis") AND TI,AB(radiographic))	55346*

Interventions	S2	TI,AB(etanercept OR enbrel OR benepali OR infliximab OR remicade OR adalimumab OR humira OR golimumab OR simponi OR simponi aria OR certolizumab pegol OR cimzia OR secukinumab OR cosentyx OR adalimumab-atto OR adalimumab-adbm OR adalimumab-adaz OR amjevita OR cyltezo OR hyrimoz OR infliximab-dyyb OR infliximab-abda OR infliximab-qbtx OR inflectra OR renflexis OR ixifi OR etanercept-szzs OR erelzi OR etanercept-ykro OR eticovo OR ustekinumab OR stelara OR ixekizumab OR taltz OR bcd-085 OR efleira OR netakimab OR apremilast OR otezla OR bimekizumab OR cdp-4940 OR ucb-4940 OR upadacitinib OR abt-494 OR filgotinib OR glpg0634 OR etoricoxib OR arcoxia OR ibi303 OR CT-P13 OR remsima OR tofacitinib OR xeljanz)	82,654*
Combination	S3	S1 AND S2	6,918*
Remove publication types not of interest	S4	S3 NOT EMB.EXACT(editorial OR “case report” OR letter OR note) OR DTYPE("Editorial" OR "Comment" OR "Letter" OR "Case Reports" OR "News" OR "Newspaper Article") OR TI,AB(“case study” or “case studies” OR “case report” OR “case reports” OR “case series”)	5454*
RCTs	S5	TI,AB(clinical trial OR RCT OR randomi*ed controlled trial OR "random allocation" OR placebo OR "double blind" OR "single blind") OR EMB.EXACT("clinical trial") OR MESH.EXACT("Clinical Trial") OR EMB.EXACT(“controlled clinical trial”) OR EMB.EXACT(“randomized controlled trial”) OR EMB.EXACT(“randomization”) OR EMB.EXACT(“single blind procedure”) OR EMB.EXACT(“double blind procedure”) OR MESH(“Clinical Trials”) OR MESH.EXACT(“Random Allocation”) OR MESH.EXACT(“Single-Blind Method”) OR MESH.EXACT(“Double-Blind Method”)	3,544,949*
SLRs or meta-analyses	S6	TI,AB(systematic review OR SLR OR “literature search” OR “meta analysis” OR “meta-analysis”) OR (TI,AB(systematic) AND TI,AB(review OR overview)) OR EMB.EXACT("systematic review") OR EMB.EXACT("literature") OR EMB.EXACT("meta analysis") OR MESH.EXACT("Systematic Review") OR MESH.EXACT("Review Literature as Topic") OR MESH.EXACT("Meta-Analysis") OR MESH.EXACT("Review")	958,134*
Combination	S7	S4 AND (S5 OR S6)	2,216 °
	S8	S7 not (rtype.exact("Conference Abstract"))	1,176°

Search conducted on April 14, 2021

* Duplicates are removed from the search but included in the result count.

° Duplicates are removed from the search and from the result count.

Table 2 Screening summary for all searches

	Hits	Duplicates	Title Abstract Screened	T/A Excluded	Full Text Review	Included	Excluded
2019.09.12	1045	5	1040	806	234	65	169
2020.08.11	91	0	91	65	26	5	21
2021.April	118	0	118	99	19	2	17
Total	**1254**	**5**	**1249**	**970**	**279**	**72**	**207**

A2. The ERG has identified several limitations in the search and screening methods reported in the main company submission. More specific details are provided in Table 2 at the end of this document. Can the company investigate and provide assurances that no relevant evidence was missed due to the following limitations?:

- ***A limited number of databases were searched i.e., a multifile search of two databases, Medline and Embase, conducted via ProQuest. Conference proceedings, HTA literature sources, grey literature sources and trials registry databases were not searched for in their own right using specialised databases.***
- ***There were weaknesses in the terms used to search for both for the interventions and diseases (see Table 113)***
- ***Non-English language papers were excluded***

For the company's systematic literature review, prior HTA submissions were reviewed to verify the collection of studies identified in this review. Conference proceedings were searched for additional information regarding RCTs identified in the review. RCTs published only in abstract form were not targeted for inclusion into the analysis due to the limitation of information contained within conference abstracts and thus were not searched separately.

The search strategy restricted results to those including treatment names in the titles or abstract. Our target study types included clinical trials and meta-analyses of these treatments, and would be specifically mentioned as an intervention. Biosimilars were

not targeted for this review since trials of biosimilars are unlikely to be compared to placebo alone.

Trials included within previous HTA submissions of AS were also reviewed to verify identification of all relevant articles. The secukinumab submission includes the Hu et al. study that we have excluded due to high potential for bias (BASDAI and BASFI outcomes only). Conversely, the secukinumab submission does not include the M3-606 study which was reported to have no outcomes of interest. We have included this trial, however, as we have identified ASDAS, BASDAI, and BASFI outcomes reported in supplementary publications.

In general, the SLR identified very similar results in comparison to previous NICE technology appraisals; please see a table for comparison below. All publications identified in the TA383 and TA407 submissions had also been identified in the SLR conducted as part of this submission (Table 3) and no publications had been missed. Furthermore, this submission also includes data from the COAST-V trial, published after TA383 and TA407.

Table 3: Trials of Adalimumab Identified in Literature Searches from the Submissions

	TA383 (2016)	TA407 (2016)	TA718 (2021)*	ID3865 (2022)
ATLAS (1, 2)	✔	✔	?	✔
COAST-V (3, 4)	X - Not available (published 2018/2019)	X - Not available (published 2018/2019)	?	✔
Hu 2012 (5)	✔ Exc. From Sensitivity analysis	✔	?	✔ Exc. From NMA due to risk of bias
Huang 2014 (6)	✔	✔	?	✔
M03-606 (7, 8)	✔	✔ - Exc. From NMA as no outcomes of interest reported	?	✔

* Included and excluded publications from TA718 could not be identified from the online sources.

Non-English language papers are usually excluded from literature searches as it is not feasible to translate these papers. In no previous Pfizer submission have non-English literature been included.

In response to the ERGs questions on search terms in Table 2 (TI,AB("axial spondyloarthritis") AND TI,AB(radiographic)) from S1 (Appendix D, p. 12) and as explained in the main company submission in section B.1.3.1, ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) are part of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Another term often used for AS is radiographic axial spondyloarthritis, therefore we felt important to also add this term to the searches, together with the term ankylosing spondylitis (please also see Table 1 above as well).

Question on the decision problem

A3. PRIORITY QUESTION: The MHRA has issued a safety update for tofacitinib, in light of data demonstrating a significantly increased risk of major adverse cardiovascular events (MACE), malignancies, serious venous thromboembolism and infections.(9, 10) This has not been mentioned in the company's submission, though the MHRA warning has important implications to this appraisal which will need to be considered by the committee. Please comment on how this may affect the use of tofacitinib on the NHS, including its proposed positioning as a 1st line therapy.

The study referred to in this safety update, ORAL Surveillance (A3921133; hereafter "Study 1133"), was a post-marketing, required safety study designed as a large, randomised, open-label clinical trial to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) versus tumour necrosis factor-alpha inhibitors (TNFi), specifically etanercept or adalimumab, in rheumatoid arthritis (RA). Study 1133 included 4,362 patients with moderate-to-severe RA aged 50 years or older and with at least one additional cardiovascular (CV) risk factor (current smoker, hypertension, HDL cholesterol <40mg/dL, diabetes mellitus, family history of premature coronary heart disease, extra-articular disease associated with RA). The co-primary endpoints of this study were non-inferiority of tofacitinib compared to TNFi with respect to major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)). The prespecified non-inferiority criteria were not met for these co-primary endpoints and the clinical trial could not demonstrate tofacitinib is non-inferior to TNF-alpha inhibitors.

On February 7, 2020, following an ad hoc analysis of Study 1133, which was then ongoing, Pfizer Europe, in agreement with EMA and the MHRA, sent a direct healthcare professional communication (DHPC) informing about the increased risk of venous thromboembolism (VTE), pulmonary embolism (PE) and serious infections in patients taking tofacitinib. A second DHPC, communicating that the co-primary endpoints for MACE and malignancy were not met, was sent on March 25, 2021 (11).

On June 10, 2021, following a review of the co-primary endpoint data from Study 1133, the Pharmacovigilance Risk Assessment Committee (PRAC) provided their recommendations to modify the tofacitinib prescribing information as regulated by EMA. The PRAC advised healthcare professionals that tofacitinib should only be used in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors, if no suitable treatment alternative is available. A further DHPC, approved by the EMA and MHRA, was distributed by Pfizer on July 23, 2021 and followed the PRAC recommendation published in June 2021.

On October 6, 2021 the MHRA published a similar drug safety update, with the advice that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives. **The summary of product characteristic (SmPC), the patient leaflet and educational risk minimisation materials for healthcare professional and patients had been updated with this information prior to the time of submission of the present NICE TA (30th November 2021), and was therefore publicly available.** These warnings, recommendations and risk minimisation measures apply to tofacitinib in all approved indications and would apply to AS in the event of MHRA approval. Importantly, **no changes were made to the MHRA approved line of therapy in existing indications** [RA, PsA, polyarticular course juvenile idiopathic arthritis (pcJIA) and ulcerative colitis (UC)] (12).

In line with this, **on October 14, 2021, the Committee for Medicinal Products for Human Use (CHMP) (Procedure No. EMEA/H/C/004214/II/0035) recommended the extension of tofacitinib indications to include treatment of adult patients**

with AS who have responded inadequately to conventional therapy (i.e. as a 1st line therapy) (13). The CHMP concluded that the overall benefit/risk of tofacitinib is positive in this indication. Importantly, the associated CHMP assessment report included a review of all safety updates from Study 1133. As the SmPC updates related to these safety updates had concluded at the time of submission, Pfizer did not consider it necessary to comment specifically on these resolved MHRA safety updates.

[redacted]

The AS clinical trial data did not demonstrate new, important safety signals in this population, although overall exposure is limited. Pfizer considers it appropriate to extrapolate the long-term safety profile of other indications (i.e. RA and PsA) and does not plan to conduct further long-term trials to gather confirmatory data in the AS population. The CHMP considered this acceptable.

As will be detailed further in Pfizer's response to question A4, incidence rates (IRs) of adverse events of special interest (AESI) were generally higher in Study 1133 compared to those observed in other tofacitinib studies in RA patients (14). This is likely due to the specific design of Study 1133, which included people with RA aged ≥50 years with at least 1 additional CV risk factor (i.e. a CV risk-enhanced population); these are also risk factors for other AESI, such as malignancy, MACE and serious infection. Incidence rates were more comparable when similar, i.e., CV risk-enriched patient subpopulations within these other studies were analysed (please refer to Pfizer's response to question A4 for further information).

As a result of the Study 1133 inclusion criteria, there are differences in the demographics and baseline characteristics between the AS, RA (excluding Study 1133) and the RA Study 1133 clinical trial populations; for example, in terms of age, gender, and baseline CV risk factors (Table 4).

Table 4.Selected Demographics and Baseline Characteristics of the AS, RA (non-A3921133), and RA Study A3921133 Clinical Populations

	Ankylosing Spondylitis (All Tofa Cohort) All Tofa[a] N = 420	Rheumatoid Arthritis (Cohort P123LTE) All Tofa[a] N = 7964	Rheumatoid Arthritis (Study A3921133) All Tofa[a] N = 2911
Age years, n (%) [a]			
N1	420	7964	2911
Mean (SD)	41.1 (11.51)	52.6 (12.1)	61.08 (6.94)
Range	20, 75	18, 86	50, 86
<65	407 (96.9)	6694 (84.1)	2020 (69.4)
≥65	13 (3.1)	1270 (15.9)	891 (30.6)
Gender, n (%)			
Male	333 (79.3)	1442 (18.1)	618 (21.2)
Female	87 (20.7)	6522 (81.9)	2293 (78.8)
Race, n (%)			
White	334 (79.5)	5170 (64.9)	2254 (77.4)
Asian	85 (20.2)	1812 (22.8)	121 (4.2)
Black	0 (0.0)	252 (3.2)	128 (4.4)
Other	1 (0.2)	730 (9.2)	408 (14.0)
BMI (kg/m^2), n (%)			
N1	419	7954	2900
Mean (SD)	26.4 (5.28)	27.1 (6.4)	29.7 (6.4)
Range	15.9, 50.6	12.08, 70.76	14.6, 65.7
<30	324 (77.1)	5816 (73.0)	1701 (58.4)
≥30	95 (22.6)	2138 (26.8)	1200 (41.2)
Geographic Region [b], n (%)			
United States/Canada	51 (12.1)	2021 (25.4)	811 (27.9)
Europe	200 (47.6)	2180 (27.4)	99 (3.4)
Latin America	-	1246 (15.6)	799 (27.4)
Asia	83 (19.8)	1775 (22.3)	-
ROW	86 (20.5)	742 (9.3)	1202 (41.3)
Smoking Status, n (%)			
Never smoked	218 (51.9)	4996 (62.7)	1487 (51.1)
Former smoker	67 (16.0)	1388 (17.4)	611 (21.0)
Current smoker	135 (32.1)	1366 (17.2)	813 (27.9)
Unknown	-	214 (2.7)	-
Baseline CRP > 2.87 mg/L, n (%)			
Yes	338 (80.5)	3157 (79.8)	2549 (87.6)
No	82 (19.5)	801 (20.2)	362 (12.4)
History of DVT and/or PE, n (%)			
Yes	8 (1.9)	NA	52 (1.8)
No	412 (98.1)	NA	2859 (98.2)
History of Coronary Heart Disease, n (%)			
Yes	2 (0.5)	30 (<1.0)	333 (11.4)
No	418 (99.5)	7934 (99.6)	2578 (88.6)
History of Myocardial Infarction, n (%)			
Yes	2 (0.5)	100 (1.3)	119 (4.1)
No	418 (99.5)	7864 (98.7)	2792 (95.9)
History of Hypertension, n (%)			
Yes	91 (21.7)	2722 (34.2)	1909 (65.6)
No	329 (78.3)	5242 (65.8)	1002 (34.4)
Baseline Diabetes, n (%)			
Yes	18 (4.3)	651 (8.2)	504 (17.3)
No	400 (95.7)	7313 (91.8)	2407 (82.7)

Source: (13, 15-17)
Study A3921119, Study A3921120, RA P123LTE studies (individual studies listed in Table 35 of the EMA assessment report (https://www.ema.europa.eu/en/documents/variation-report/xeljanz-h-c-004214-ii-0035-epar-assessment-report-variation_en.pdf), Study A3921133, Study A3921133

Table 4.Selected Demographics and Baseline Characteristics of the AS, RA (non-A3921133), and RA Study A3921133 Clinical Populations

	Ankylosing Spondylitis (All Tofa Cohort) All Tofa[a] N = 420	Rheumatoid Arthritis (Cohort P123LTE) All Tofa[a] N = 7964	Rheumatoid Arthritis (Study A3921133) All Tofa[a] N = 2911

a. Received at least one dose of tofacitinib for AS All Tofa Cohort and RA P123LTE Cohort, and IR 5 mg BID or 10 mg BID in Study A3921133.
b. ROW included Asian countries in Study A3921133.
Abbreviations: AS = ankylosing spondylitis; BID = twice daily; BMI = body mass index; CRP = C-reactive protein; DVT = deep vein thrombosis; IR = immediate release; LTE = long term extension; n = number of patients meeting a criterion; N = number of patients included in the safety analysis set; N1 = number of patients included in the analysis; NA = not available; P = phase; PE = pulmonary embolism; RA = rheumatoid arthritis; ROW = rest of the world; SD = standard deviation; Tofa = tofacitinib.

Incidence rates for AESI, including cardiovascular events, malignancies and serious infections, have previously been reported for the tofacitinib clinical programme for several indications, including RA, PsA, UC and psoriasis (PsO) (18). In this exploratory analysis, IRs of serious adverse events (SAEs) were higher in RA patients compared to other diseases. Similarly, IRs of discontinuation due to adverse events were higher for RA patients compared to other disease cohorts: 7.2 (6.9-7.6), 3.8 (3.0-4.8), 4.1 (3.3-4.9) and 5.7 (5.3-6.3) for RA, PsA, UC and PsO, respectively. In general, patients in the non-RA cohorts were younger and had a lower exposure to corticosteroids. Therefore, accounting for the demographic and clinical characteristics of AS patients, long-term IRs of SAEs and treatment discontinuation due to adverse events in tofacitinib-treated AS patients may be expected to be relatively lower than those observed in RA patients.

In conclusion, the benefit/risk of the proposed recommended use of tofacitinib 5mg BID in AS patients who have failed conventional treatment remains favorable when used in accordance with the relevant risk minimisation measures. **Pfizer does not anticipate the safety update to substantially affect the population addressed in the current NICE appraisal or the decision problem. As explained later in response to question A5a, based on the demographic and clinical characteristics of AS patients in studies A3921119 and A3921120 as well as the mean age and prevalence of comorbidities observed in real word data (21, 22), Pfizer anticipates a significant proportion of patients with AS to still be eligible for tofacitinib after failure to conventional therapy despite latest MHRA updates (please also see data presented in Table 7). In addition, the decision problem is considering the use of tofacitinib across first and subsequent lines of treatment**

(please see response to A5b for rationale on the use of adalimumab as the most relevant comparator across all treatment lines).

For patients with AS, choice of advanced treatment options is currently limited, particularly with respect to route of administration. The availability of tofacitinib as the first oral advanced therapy tor AS (vs existing subcutaneous/intravenous) allows patients and their clinicians more freedom to consider and meet their individual needs and preferences. As expressed in previous appraisals, having a greater choice of treatments would be particularly valuable to people with this condition, allowing them and their clinicians to choose treatments that take into account their individual needs and preferences and giving them a feeling of more control over their condition.

A4. PRIORITY QUESTION: Please provide a summary of the tofacitinib safety data relating to the increased risk of MACE, pulmonary embolism, deep vein thrombosis, venous thromboembolism, arterial thromboembolism, malignancies, serious infections and all-cause mortality, and how it compares with data for anti-TNFs.

The safety profile of tofacitinib has been previously reported and a summary is included in the current SmPC (12), which incorporates the safety updates arising from Study 1133 specifically relating to VTE, PE, serious infections, MACE and malignancies.

Overview

One large, randomised, open-label safety study (Study 1133, detailed in Pfizer's response to question A3) provides a direct comparison between two doses of tofacitinib (5mg twice daily and 10mg twice daily) versus TNF-inhibitors (adalimumab or etanercept). In this response we will first summarise the AS safety data and those originating from studies of tofacitinib in other inflammatory arthritides (RA and PsA), before addressing Study 1133 and real-world studies in which tofacitinib has been specifically studied alongside TNFi comparators (12).

Safety data from the tofacitinib clinical trial programmes in chronic inflammatory arthritis

In the AS clinical trial programme, no cases of death, malignancies, NMSC, CV events (MACE, thrombosis [ATE, PE, and DVT]), GI perforation, or rhabdomyolysis were observed. In Study 1120 (pivotal study for AS), one, non-opportunistic, serious infection was reported (17). No malignancies occurred in the tofacitinib 5mg group in 1119. Five ongoing cardiac disorders were reported in 1119 in the tofacitinib 5mg group, though it was not possible to ascertain whether these occurred after study initiation. One serious infection was observed (16).

The safety databases from the RA and PsA development programmes (excluding Study 1133) provide context for the incidence rates and range of AEs reported with tofacitinib treatment in the AS programme. However, caution should be exercised in interpretation due to differences relating to the design of the RA (monotherapy and background csDMARD) and PsA (background csDMARD only) programmes. Details can be found as part of the recent CHMP extension of indication variation assessment report (30 September 2021, EMA/CHMP/553425/2021, CHMP).

In summary, when the IRs for SAEs and AESI in patients treated with tofacitinib in the AS development programme are compared to those observed in the PsA and RA programmes, IRs in the AS patients are generally lower compared to the other two conditions. An exception is observed in the incidence of herpes zoster, which was higher in AS patients (2.68/100 patient years [PY]) compared to PsA (1.76/100 PY) but lower compared to RA (3.58/100 PY). The differences in IRs between the AS clinical program and the IRs observed in the RA and PsA clinical programmes should be interpreted with caution due to lower patient numbers and limited tofacitinib exposure in the AS programme.

The table below summarises the IRs (number of patients with event per 100 PYs) (with 95% CIs) for SAEs, all-cause mortality and AESI in patients treated with tofacitinib 5 mg BID in AS (randomised phase 2 and 3 studies), PsA (randomised phase 3 studies, Cohort 2) and RA (randomised phase 2 and 3 studies) clinical trial programmes (while on treatment estimand)

Table 5. IRs in patients treated with tofacitinib 5 mg BID in AS, PsA and RA clinical trial programmes

Adverse Events	Ankylosing Spondylitis (All Tofa Cohort) All Tofa 5 mg BID[a] N = 316 Exposure (patient-years) = 208.90				Psoriatic Arthritis (Cohort 2a) All Tofa 5 mg BID[a] N = 347 Exposure (patient-years) =196.2				Rheumatoid Arthritis (Cohort P2P3) Tofa 5 mg BID[b] N = 2664[c] Exposure (patient-years) = 2476.66			
	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY
SAEs	8	2.53	229.39	3.49 (1.51, 6.87)	15	4.3	198.14	7.57 (4.24, 12.49)	242	9.1	2487.66	9.73 (8.54, 11.03)
Serious infections	1	0.32	231.28	0.43 (0.01, 2.41)	4	1.2	200.74	1.99 (0.54, 5.10)	67	2.5	2570.31	2.61 (2.02,3.31)
OI[d,e]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.84	0.50 (0.01, 2.77)	9	0.3	2582.80	0.35 (0.16,0.66)
TB[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	2	0.1	2584.24	0.08 (0.01,0.28)
HZ	5	1.58	229.74	2.18 (0.71, 5.08)	3	0.9	199.58	1.50 (0.31, 4.39)	74	2.8	2535.74	2.92 (2.29,3.66)
Malignancies excluding NMSC[d]	0	0	231.35	0.00 (0.00, 1.59)	3	0.9	200.76	1.49 (0.31, 4.37)	9	0.3	2583.73	0.35 (0.16,0.66)
Lymphoma[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	0	0	2584.41	0.00 (0.00,0.14)
NMSC[d]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	11	0.4	2578.26	0.43 (0.21,0.76)
MACE[d]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.10	0.50 (0.01, 2.77)	7	0.3	2500.08	0.28 (0.11,0.58)
DVT[f]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	4	0.2	2581.36	0.15 (0.04,0.40)
PE[f]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	3	0.1	2583.34	0.12 (0.02,0.34)
ATE[f]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.76	0.50 (0.01, 2.78)	6	0.2	2582.94	0.23 (0.09, 0.51)
VTE[f,g]	0	0	231.35	0.00 (0.00, 1.59)	0	0	201.10	0.00 (0.00, 1.83)	7	0.3	2580.29	0.27 (0.11,0.56)
Thrombosis[f,h]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	200.76	0.50 (0.01, 2.78)	13	0.5	2578.82	0.50 (0.27,0.86)
GI perforation[d]	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.02	0.50 (0.01, 2.77)	0	0	2584.41	0.00 (0.00,0.14)
ILD[i]	0	0	231.35	0.00 (0.00, 1.59)	0	0.0	201.10	0.00 (0.00, 1.83)	3	0.1	2583.22	0.12 (0.02,0.34)
All-cause mortality	0	0	231.35	0.00 (0.00, 1.59)	1	0.3	201.10	0.50 (0.01, 2.77)	8	0.3	2584.41	0.31 (0.13,0.61)
All-cause mortality (all Event Last Dose Algorithm)[j]	0	0	261.97	0.00 (0.00, 1.41)	NA	NA	NA	NA	15	0.6	2584.41	0.58 (0.32,0.96)

Source: (13), Table 78.

a. Includes the data from subjects who were randomised to tofacitinib 5 mg IR BID and the tofacitinib-treated period for the subjects who were randomised to the placebo → tofacitinib 5 mg IR BID.
b. Includes the data from subjects who were randomised to tofacitinib 5 mg IR BID.
c. N value for MACE is 2401
d. Adjudicated events in all studies.
e. Opportunistic infections exclude Tuberculosis.
f. Adjudicated events in AS studies only.
g. VTE includes DVT and/or PE.
h. Thrombosis includes DVT, PE and/or ATE.
i. Adjudicated events by a Pfizer Internal Review Committee.
j. The numerator counts all the events occurred either on- or off-treatment, while PY (the denominator) is calculated to subject's Treatment Policy Risk Period in AS and subject's last dose + 28 days in RA.
Exposure is the sum of treatment exposures of all the subjects in the group. Risk period is to subject's last dose + 28 days or to the end of the cohort. Events are counted within the risk period. PY (in patient-year) is the sum of the times to the first event for subjects with event or to the end of the risk period for subjects without event and is the denominator for the incidence rate calculation.
Incidence rate is a naïve estimate without adjusting for study. Exact Poisson (adjusted for PY) 95% CI is provided for the Incidence rate.
AS All Tofa Cohort All Tofa 5 mg BID group includes completed randomised Phase 2 Study A3921119 and Phase 3 Study A3921120.
PsA Cohort 2a All Tofa 5 mg BID group includes completed randomised Phase 3 Studies A3921091 and A3921125.
RA Cohort P2P3 Tofa 5 mg BID group includes completed randomised Phase 2 and 3 Studies A392-1019, 1025, 1032, 1035, 1039, 1040, 1044 (2 years), 1045, 1046, 1064, 1068, 1069 (2 years), 1073, 1129, 1187 and 1237.

The table below summarises the IRs (number of patients with event per 100 PYs) (with 95% CIs) of SAEs, all-cause mortality and AESI in patients treated with all tofacitinib doses in AS (randomised phase 2 and 3 studies), PsA (randomised phase 3 studies, Cohort 3) and RA (randomised phase 1, phase 2, phase 3 and open-label long-term extension studies) clinical trial programmes (while on treatment estimand).

Table 6. IRs in patients treated with all tofacitinib doses in AS, PsA and RA clinical trial programmes

Adverse Events	Ankylosing Spondylitis (All Tofa Cohort) All Tofa N = 420 Exposure (patient-years) = 232.98				Psoriatic Arthritis (Cohort 3) All Tofa N = 783 Exposure (patient-years) = 2037.97				Rheumatoid Arthritis (Cohort RA P123LTE) All Tofa N = 7964 Exposure (patient-years) =23496.73			
	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY	n	%	PY	Incidence rate (95% CI) Per 100 PY
SAEs	9	2.14	260.64	3.45 (1.58, 6.55)	135	17.2	1938.22	6.97 (5.84, 8.24)	1913	24.0	21361.14	8.96 (8.56, 9.37)
Serious infections	1	0.24	262.75	0.38 (0.01, 2.12)	24	3.1	2091.93	1.15 (0.74, 1.71)	592	7.4	23883.77	2.48 (2.28, 2.69)
OI[a,b]	0	0	262.82	0.00 (0.00, 1.40)	7	0.9	2089.54	0.34 (0.13, 0.69)	133	1.7	24054.65	0.55 (0.46, 0.66)
TB[a]	0	0	262.82	0.00 (0.00, 1.40)	0	0.0	2099.94	0.00 (0.00, 0.18)	38	0.5	24134.75	0.16 (0.11, 0.22)
HZ	7	1.67	260.89	2.68 (1.08, 5.53)	36	4.6	2045.98	1.76 (1.23, 2.44)	795	10.0	22198.96	3.58 (3.34, 3.84)
Malignancies excluding NMSC[a]	0	0	262.82	0.00 (0.00, 1.40)	15	1.9	2098.40	0.71 (0.40, 1.18)	179	2.2	24108.42	0.74 (0.64, 0.86)
Lymphoma[a]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	12	0.2	24137.17	0.05 (0.03, 0.09)
NMSC[a]	0	0	262.82	0.00 (0.00, 1.40)	16	2.0	2076.76	0.77 (0.44, 1.25)	133	1.7	23860.11	0.56 (0.47, 0.66)
MACE[a]	0	0	262.82	0.00 (0.00, 1.40)	6	0.8	2095.81	0.29 (0.11, 0.62)	85	1.2	22966.82	0.37 (0.30, 0.46)
DVT[c]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	37	0.5	24083.96	0.15 (0.11, 0.21)
PE[c]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2098.46	0.05 (0.00, 0.27)	31	0.4	24107.10	0.13 (0.09, 0.18)
ATE[c]	0	0	262.82	0.00 (0.00, 1.40)	7	0.9	2086.35	0.34 (0.13, 0.69)	85	1.1	23957.05	0.35 (0.28, 0.44)
VTE[c,d]	0	0	262.82	0.00 (0.00, 1.40)	2	0.3	2098.38	0.10 (0.01, 0.34)	61	0.8	24064.63	0.25 (0.19, 0.33)
Thrombosis[c,e]	0	0	262.82	0.00 (0.00, 1.40)	9	1.1	2084.79	0.43 (0.20, 0.82)	145	1.8	23887.58	0.61 (0.51, 0.71)
GI perforation[a]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.86	0.05 (0.00, 0.27)	27	0.3	24135.92	0.11 (0.07, 0.16)
ILD[f]	0	0	262.82	0.00 (0.00, 1.40)	1	0.1	2099.59	0.05 (0.00, 0.27)	45	0.6	24084.98	0.19 (0.14, 0.25)
All-cause mortality	0	0	262.82	0.00 (0.00, 1.40)	2	0.3	2099.94	0.10 (0.01, 0.34)	59	0.7	24139.28	0.24 (0.19, 0.32)
All-cause mortality (all Event Last Dose Algorithm)[g]	0	0	297.13	0.00 (0.00, 1.24)	7	0.9	2037.38	0.34 (0.14, 0.71)	121	1.5	24139.28	0.50 (0.42, 0.60)

Source: (13), Table 79.

a. Adjudicated events in all studies.
b. Opportunistic infections exclude Tuberculosis.
c. Adjudicated events in AS studies only.
d. VTE includes DVT and/or PE.
e. Thrombosis includes DVT, PE and/or ATE.
f. Adjudicated events by a Pfizer Internal Review Committee.
g. The numerator counts all the events occurred either on- or off-treatment, while PY (the denominator) is calculated to subject's Treatment Policy Risk Period in AS, subject's last dose in PsA and subject's last dose + 28 days in RA.
Exposure is the sum of treatment exposures of all the subjects. Risk period is to subject's last dose + 28 days or to the end of the cohort except for all-cause mortality (all event last dose algorithm) noted above. Events are counted within the risk period.
PY (in patient-year) is the sum of the times to the first event for subjects with event or to the end of the risk period for subjects without event and is the denominator for the incidence rate calculation.
Incidence rate was a naïve estimate without adjusting for study. Exact Poisson (adjusted for PY) 95% CI is provided for the incidence rate.
AS All Tofa Cohort All Tofa group includes completed randomised Phase 2 Study A3921119 and Phase 3 Study A3921120.
PsA Cohort 3 All Tofa group includes completed randomised Phase 3 Studies A3921091, A3921125 and LTE Study A3921092.
RA Cohort RA P123LTE All Tofa group includes completed randomised Phase 2, 3 and LTE Studies A392-1019, 1024 (LTE), 1025, 1032, 1035, 1039, 1040, 1041 (LTE), 1044 (2 years), 1045, 1046, 1064, 1068, 1069 (2 years), 1073, 1109, 1129, 1130, 1152, 1187, 1192, 1215, and 1237.

Other safety data (including post-marketing experience with tofacitinib) and comparison with TNFi

Details of the data from Study 1133 (please refer to question A3 for study background) for the safety updates regarding MACE and malignancies in the cardiovascular (CV) risk-enriched RA population can be found in the PRAC assessment from June 2021 (ema/prac/333216/2021) and in relevant direct healthcare professional communications (DHCP letters) distributed on:

- February 7, 2020
- March 25, 2021
- July 23, 2021

For thrombotic events (including DVT, ATE and PE), serious infections, and all-cause mortality, details of the IRs observed in tofacitinib groups versus TNFi in the CV risk-enriched RA population (Study 1133), as well as IRs of thrombotic events, MACE, serious infections and mortality from other studies making up the tofacitinib development trial programme (phase 1, phase 2, phase 3 and open-label long term extension studies) for RA can be found in the PRAC report published by EMA in October 2019 (19), and in the DHCP letter (11). In addition, comprehensive integrated safety summaries of tofacitinib from the clinical trial programme in RA and other indications are available. A comprehensive summary relating specifically to the risk of venous and arterial thrombosis has also been published (3, 14, 18).

In general, the IRs of AESIs were generally higher in Study 1133 relative to other tofacitinib studies in the RA population. However, as mentioned previously, this is not unexpected based upon the study design, which included people with RA aged ≥50 years with at least 1 additional CV risk factor, which are risk factors for other AESI, such as malignancy, MACE and serious infection. Incidence rates were more comparable when similar, ie, CV risk-enriched patient populations, for these other studies were analysed. The figures below show the non-head-to-head comparison for MACE and malignancies between study 1133, non-study 1133 overall cohorts and the non-study 1133, CV risk-enriched RA populations:

Figure 1: Incidence Rates for MACE in Tofacitinib RA Clinical Programme (not a head-to-head comparison) (please note this figure contains AIC information)

a: Proportions and Incidence Rates for Adjudicated MACE - RA P123LTE (Average Dosing) (Final Data 18JAN2019) (28-Day IR Algorithm) RA population, not CV-enriched
b: Non 1133 cv+: Table 1582.2.1.4. Proportions and Incidence Rates for Adjudicated MACE by Baseline Cardiovascular Risk Factor - RA P123LTE (Average Dosing) (Final Data 18JAN2019) (28-Day IR Algorithm). CV-enriched RA population from tofacitinib RA studies excl 1133

c: Adjudicated MACE Based on Univariate Cox Proportional Hazard Model (SAS, 60-Day On-Treatment Time). 60-Day On-Treatment Time: the risk period is the minimum of (last contact date, or Last Study Treatment Dose date +60 days);
d: Adjudicated MACE Based on Univariate Cox Proportional Hazard Model (SAS, 28-Day On-Treatment Time)

Figure 2: Incidence Rates for Malignancies (Excluding NMSC) in the Tofacitinib RA Clinical Programme (not a head-to-head comparison) (please note this figure contains AIC information)

a. CP-690,550 P123LTE. Cut-off Date: 02March2017. Data on file. Pfizer Inc, New York, NY.
b. Data on file. Pfizer Inc, New York, NY.
ISS = Tofacitinib RA Integrated Safety Summary

The ENTRACTE trial (which preceded Study 1133) was designed to compare the risk of MACE among CV risk-enriched RA patients randomized to tocilizumab (TOC) or etanercept (ETN). That trial was designed and executed as a post-marketing requirement of the US FDA for TOC. ENTRACTE had a similar study design and duration of follow up as Study 1133, and the study population (moderate-to-severe RA patients aged 50 and older with at least one additional CV risk factor) had a similar distribution of key baseline characteristics to the Study 1133 populations. In ENTRACTE, the prespecified primary endpoint was time to first occurrence of MACE (defined in the same way as in in Study 1133). A total of 3,080 patients with RA were enrolled; 1,538 were randomly assigned to the TOC arm and 1,542 were randomly assigned to the ETN arm, and the mean follow-up time was 3.2 years. Overall, the IRs for MACE, total myocardial infarction and non-fatal myocardial infarction observed in the ENTRACTE study were higher both for ETN and TOC than the IRs found for TNFi in Study 1133, and similar or higher than the IRs in the tofacitinib-treated groups in Study 1133. The IRs of malignancies excluding NMSC (not a primary endpoint of the

study) in the ENTRACTE Study observed in ETN-treated group were consistent with those found in TNFi-treated subjects in Study 1133

Figure 3: Incidence Rates of MACE in Study 1133 and ENTRACTE Study (not a head-to-head comparison) (please note this figure contains AIC information)

a. Adjudicated MACE Based on Univariate Cox Proportional Hazard Model (SAS, 60-Day On-Treatment Time). 60-Day On-Treatment Time: the risk period is the minimum of (last contact date, or Last Study Treatment Dose date +60 days).
b. ITT (total time) population. Giles et al (2019).
Data on file. Pfizer Inc, New York, NY.

Figure 4: Incidence Rates of Malignancies (excl NMSC) in Study 1133 and ENTRACTE Study (not a head-to-head comparison) (please note this figure contains AIC information)

a. Adjudicated Malignancies Excluding NMSC Based on Univariate Cox Proportional Hazard Model (SAS, Total Time Analysis). Data on file. Pfizer Inc, New York, NY.
b. Giles et al (2019). The ENTRACTE, the prespecified primary endpoint was time to first occurrence of MACE (defined in the same way as in in Study A3921133), but not malignancies. A total of 3,080 patients with RA were enrolled; 1,538 were randomly assigned to the TOC arm and 1,542 were randomly assigned to the ETN arm, and the mean follow-up time was 3.2 years
Data on file. Pfizer Inc, New York, NY.

Finally, real word data from a post-authorisation safety study embedded in the CorEvitas RA registry in the US compared 5-year safety data of tofacitinib versus biologic disease anti-rheumatic drugs (bDMARDs) in the overall RA population, showing similar incidence rates for MACE, serious infections, malignancy, venous

thromboembolism, deep vein thrombosis, pulmonary embolism and deaths between tofacitinib-treated patients compared to bDMARDs-treated patients (20).

Figure 5: Incidence Rates of Selected Adverse Events in PS-Trimmed Population (please note this figure contains AIC information)

Graph adapted from (20).
IR=Incidence rates are number of first events/100 PY of outcomes in the PS-trimmed population; incidence rates were based on different definitions of the risk window for outcomes with acute onset (MACE, SIEs, HZ) or latent onset (malignancies and death). Patients initiated treatment as monotherapy or in combination with a csDMARD.
†XELJANZ cohort primarily received 5 mg BID.
‡bDMARD cohort included patients initiating adalimumab, certolizumab pegol, golimumab, etanercept, infliximab, abatacept, anakinra, rituximab, or tocilizumab.
§MACE defined as myocardial infarction, stroke/transient ischemic attack, and cardiovascular death.
AE=adverse event; bDMARD=biologic disease-modifying antirheumatic drug; BID=twice daily; CI=confidence interval; csDMARD=conventional synthetic disease-modifying antirheumatic drug; HZ=herpes zoster; MACE=major adverse cardiovascular events; NMSC=nonmelanoma skin cancer; PS=propensity score; PY=patient years; SIE=serious infection event.

Figure 6:Age and Gender-Standardised Rates of VTE, DVT, and PE (please note this figure contains AIC information)

Graph adapted from Kremer JM, et al. 2021. ACR Open Rheumatol. 2021;doi: 10.1002/acr2.11232
Age- and gender-standardized IRs are number of first events/100 PY of VTE events; incidence rates were based on the definition of the risk window for outcomes with acute onset. Age- and gender-standardized incidence rates were estimated using direct standardization (XELJANZ population used as standard population); VTE data did not have 80% or more power to detect a HR of 2.25 or less between cohorts. Propensity scores were not calculated. Patients initiated treatment as monotherapy or in combination with a csDMARD. †XELJANZ cohort primarily received 5 mg BID. ‡bDMARD cohort included patients initiating adalimumab, certolizumab pegol, golimumab, etanercept, infliximab, abatacept, anakinra, rituximab, or tocilizumab.
bDMARD=biologic disease-modifying antirheumatic drug; BID=twice daily; CI=confidence interval; Corrona=Consortium of Rheumatology Researchers of North America, Inc; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DVT=deep vein thrombosis; HR=hazard ratio; PE=pulmonary embolism; PY=patient years; VTE=venous thromboembolism.
Sources: (20). Data on file. Pfizer Inc., New York, NY.

In conclusion, while the coprimary endpoints of Study 1133 in a CV risk-enriched population in RA were not met (i.e. neither tofacitinib 5 mg twice daily or 10mg twice daily demonstrated non-inferiority with respect to TNFi for the endpoints MACE and malignancy [excluding NMSC]), analyses of data from PsA, AS, PsO and UC populations, as well as in the non-CV risk-enhanced RA population, have not shown an increased risk for tofacitinib therapy versus TNFi for these AEs. Similarly, while ad hoc analyses of Study 1133 have shown increased rates of VTE, PE, serious infections and mortality, these findings have not been replicated in non-CV risk-enhanced populations. With the current labelling and risk minimisation, Pfizer believes that the risk/benefit profile for tofacitinib in eligible AS patients to be positive.

A5. PRIORITY QUESTION: The MHRA safety update states that tofacitinib should not be used in people over 65 years of age, current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors, unless there are no suitable treatment alternatives.(10)

a) Please comment on how the restrictions may affect the representativeness of the trial populations in relation to those currently eligible for treatment, and any implications for trial effect estimates;

Pfizer does not anticipate this to substantially affect the population addressed in the current NICE appraisal or the decision problem. The restrictions in the use of tofacitinib introduced following the recent drug safety updates by MHRA will apply equally to future indications for tofacitinib, including AS. Treatment choice should be therefore individualised, taking into consideration the approved risk minimisation measures for the use of tofacitinib (available at https://www.medicines.org.uk/emc/product/2500/) (12). Based on the demographic and clinical characteristics of AS patients in studies A3921119 and A3921120 as well as the mean age and prevalence of comorbidities observed in real word data (21, 22), Pfizer anticipates a significant proportion of patients with AS to still be eligible for tofacitinib after failure to conventional therapy despite latest MHRA updates.

In the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS), of 994 participants, 671 did not have any comorbidities, with a mean

age of 43.0 (12.7); 394 of these (59%) met modified New York criteria for AS and 351 (40%) were classified as having never smoked. Comorbidities analysed included ischaemic heart disease, heart failure, stroke, hypertension, diabetes, asthma, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, liver disease, renal disease, depression, cancer, tuberculosis (TB) and demyelinating disease (22).

Table 7: Baseline Characteristics of A3921120 and Patients Recruited into the BSRBR-AS Registry

	A3921120		BSRBR-AS (n=994)
	Tofacitinib (n=133)	Placebo (n=136)	
Age			
Mean age, years (SD)	42.2 (11.9)	40.0 (11.06)	44.7 (13.4)
<65 years, n (%)	127 (95.5)	136 (100)	-
≥65 years, n (%)	6 (4.5)	0	-
Smoking Status			
Current, n (%)	34 (25.6)	44 (32.4)	241 (27)
Former, n (%)	24 (18.0)	19 (14.0)	291 (33)
Never Smoked, n (%)	75 (56.4)	73 (53.7)	351 (40)
Cardiovascular Risk Factors			
Hypertension, n (%)	26 (19.5)	25 (18.4)	- (11)
Diabetes mellitus, n (%)	7 (5.3)	5 (3.7)	- (2.5)
Ischaemic heart disease, n (%)	1 (0.8)	2 (1.5)	- (1.5)
Stroke, n (%)	-	-	- (0.7)
Heart Failure, n (%)	-	-	- (0.6)

Source: (17, 22)

ASAS40 outcomes for patients receiving tofacitinib vs. placebo were compared by age and smoking status (see Table 8). No patients aged 65 years or above were included in the placebo arm of A3921120 and so ASAS40 outcomes could not be compared with tofacitinib. However, one-third (2 out of 6 patients) of patients aged ≥65 years and receiving tofacitinib achieved an ASAS40 response. Patients treated with tofacitinib achieved improved ASAS40 responses compared with placebo, regardless of smoking status. Sixteen (of 34; 47.1%) current and 9 (of 24; 37.5%) former smokers achieved an ASAS40 response after treatment with tofacitinib, compared with 11.4% and 15.8% for placebo. These rates were in line with patients who had never smoked (38.7% and 12.3% respectively), suggesting that tofacitinib is an efficacious treatment option for AS, regardless of smoking status. Although the

study was not specifically powered to detect differences based on age or smoking status, the results show similar benefits across these subgroups. Outcomes by cardiovascular disorder or malignancy risk factors had not been assessed.

Table 8: ASAS40 Outcomes by Age and Smoking Status (A3921120)

Category at Baseline		Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
		N	n	R (%)	N	n	R (%)	
Age	<65 years	127	[redacted]	[redacted]	136	[redacted]	[redacted]	[redacted]
	≥65 years	6	[redacted]	[redacted]	0	[redacted]	[redacted]	-
Smoking Status	Never	75	[redacted]	[redacted]	73	[redacted]	[redacted]	[redacted]
	Former	24	[redacted]	[redacted]	19	[redacted]	[redacted]	[redacted]
	Current	34	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]

Source: (17)

b) Given the above, the ERG's clinical advisors indicate that tofacitinib is very unlikely to be used early in the treatment pathway, and may only be considered in patients for whom no suitable treatment alternative exists. This is not aligned with the positioning proposed in the main company submission. Please comment on how tofacitinib may be used in clinical practice under the MHRA safety update;

As detailed in the response to previous questions (A3 and A5a), Pfizer believes that a substantial population of AS patients will not have risk factors requiring therapeutic alternatives to be exhausted and therefore will be eligible for tofacitinib as earlier line of therapy. In line with the marketing authorisation, tofacitinib can be used as first or subsequent line of therapy and this has been the positioning proposed in the main company submission.

Treatment choice is largely driven by informed discussion and consensus between the prescribing clinician and the patient, based on the level of disease activity, patient risk tolerance, patient preference, and patient lifestyle considerations. As an oral JAK inhibitor, tofacitinib provides an alternative treatment option for people with active AS for whom NSAIDs have been insufficiently effective or not tolerated, with a route of administration that eliminates the physical and psychological patient burden of injections. Studies have shown that patients with other rheumatological conditions

prefer oral therapies over injectables due to ease of administration (23), however, current AS treatment options are limited to SC and IV.

In A3921119 and A3921120 trials, tofacitinib showed greater ASAS20, ASAS40 and BASDAI50 response rates compared with placebo at Week 12 and Week 16. In A3291120, tofacitinib showed significant reduction in disease activity compared with placebo, and significant alleviation of back pain in as early as 2 weeks. Efficacy and improvements in HRQoL were demonstrated in up to 48-weeks follow-up. Tofacitinib was also consistently efficacious across subgroups of prior treatment history (biologic-naïve and biologic experienced), as assessed by ASAS20 and ASAS40 response rates (see response to questions A7b and A13).

The NMA described in the submission incorporates the key clinical outcomes and outcomes used in the cost effectiveness models of past HTAs (TA383, TA407 and TA718; see Section B2). This NMA showed that there were no statistically significant differences between tofacitinib and adalimumab across all efficacy and HRQoL outcomes in mixed (biologic experienced and biologic naïve) and biologic naïve populations.

Pfizer considers that adalimumab is the most relevant comparator, irrespective of line of therapy because it is the most prescribed bDMARD in AS, has demonstrated similar health benefits to other TNFis and IL-17is in previous NICE appraisals and is likely to have the cheapest net price, as biosimilar versions are available in the UK. However, in response to the request of the ERG question A13 and to remove the uncertainty around the use of tofacitinib subsequent line of therapy, we provide NMA results for the comparison with IL-17s. The results shown no statistically significant difference between tofacitinib and IL-17s. Hence, tofacitinib can be considered similarly clinically effective as other treatment options for AS. In addition, we have added IL-17 to our updated base case of the cost-comparison, to provide further evidence that consideration of additional comparators does not change the decision problem (please also see response provided for questions B3 and B7).

Besides, in line with the marketing authorisation, tofacitinib can be used as first or subsequent line of therapy. Using a sequence of treatments is common in AS and

rechallenging patients with TNFs is also frequent, therefore a comparison with TNF inhibitor ADA is reasonable to reflect tofacitinib's position in the treatment pathway.

c) ***Please comment on how effect estimates for tofacitinib compare to effect estimates for IL-17s, particularly secukinumab and ixekizumab which are also recommended by NICE in this indication, for biologic-experienced patients.***

The safety results of the NMA for the comparison of tofacitinib with secukinumab are presented under question A13. The results demonstrate that there is no statistically significant difference between secukinumab and tofacitinib in terms of safety endpoints.

d) ***Please comment on the possibility of increased discontinuation, and consequent reduction of time on treatment, from the development of risk factors while on treatment with tofacitinib (for example, increased lipid levels).***

In trial A3921120, with follow up periods up to 48 weeks, the most common reasons for discontinuation of treatment due to adverse events were liver enzyme investigations, infections and infestations, and gastrointestinal disorders, as shown in the table below:

Figure 7:Discontinuation of Study Drug Due to Adverse Events in Study A3921120 (please note this figure contains AIC information)

a. Patients who discontinued study drug were expected to continue with all regularly scheduled visits for safety and efficacy assessments. B. Patient discontinued from the study. AE=adverse event; BID=twice daily; SAE=serious adverse event.
Source: Data on file. Pfizer Inc., New York, NY.

In line with the question asked, we have summarised the findings in lipid levels, blood pressure and weight gain as potential emergent cardiovascular risk factors in study A3921120, with a total follow up period of up to 48 weeks.

Lipids were influenced by tofacitinib treatment, in particular a mild increase in total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were observed (data for triglycerides not shown) (24). Of note, cholesterol levels remained stable from week 16 to week 48, and HDL-cholesterol (lower levels associated with CV risk) increased in tofacitinib-treated patients during the study period.

Figure 8: Mean cholesterol (mg/dL) assessed at fasting stage up to week 48 (please note this figure contains AIC information)

Graph adapted from (24)
b. Patients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (dashed line).
BID=twice daily; N=number of patients in safety analysis set; N1=number of patients with observation at visit; SE=standard error.

Figure 9: Mean HDL cholesterol (mg/dL) assessed at fasting stage up to week 48 (please note this figure contains AIC information)

Graph adapted from (24)
b. Patients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (dashed line).
BID=twice daily; HDL=high density lipoprotein; N=number of patients in safety analysis set; N1=number of patients with observation at visit; SE=standard error.

Figure *10*: Mean LDL cholesterol (mg/dL) assessed at fasting stage up to week 48 (please note this figure contains AIC information)

Graph adapted from (24)
b. Patients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (dashed line).
BID=twice daily; LDL=low density lipoprotein; N=number of patients in safety analysis set; N1=number of patients with observation at visit; SE=standard error.

The findings on cholesterol levels from study A3921120 are in line with those observed in a previous pooled study of phase III studies in patients with rheumatoid arthritis, in which tofacitinib was associated with increases in total cholesterol, LDL-cholesterol and HDL-cholesterol, which peaked at approximately 6 weeks and remained stable

during the 2 years follow-up in clinical trials (25). Current tofacitinib label recommends assessment of lipid parameters to be performed after 8 weeks following initiation of tofacitinib therapy (12). Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pre-treatment levels with statin therapy.

No clinically significant changes were observed in sitting blood pressure up to 16 weeks of the placebo-controlled period in patients taking tofacitinib, and also at the end of the 48 weeks in the uncontrolled period in study A3921120 (17).

Figure 11: Mean Systolic and Diastolic Blood Pressure (mmHg) up to Week 48 (please note this figure contains AIC information)

Data are from the Week 48 final analysis. aPatients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (vertical dashed line). Δ=change from BL; BID=twice daily; BL=baseline; BP, blood pressure;
n=number of patients evaluable for the vital sign at a visit; N=number of patients in safety analysis set; SD=standard deviation.
Data on file. Pfizer Inc., New York, NY

A mild increase in body weight was observed in study A3921120 among tofacitinib-treated patients, particularly during the first weeks of treatment, with a mean increase of 2.2 kg at week 48. Similar increases have been observed in the rheumatoid arthritis (RA) and psoriatic arthritis (PsA) clinical programmes.

Figure 12: Mean Weight Change up to Week 48 (please note this figure contains AIC information)

Data are from the Week 48 final analysis. a. Patients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (vertical dashed line). Δ=change from BL; BID=twice daily; BL=baseline; n=number of patients evaluable for the vital sign at a visit; N=number of patients in safety analysis set; SD=standard deviation.
Data on file. Pfizer Inc., New York, NY.

Population-based data relating to the increase in CV risk over time in the British AS population exist (26). However, it is unclear to what degree this reflects the increased prevalence of each of the contributing CV risk factors over time. The observed higher CV morbidity in AS patients compared to the general population is a common phenomenon across most inflammatory rheumatological conditions, and is a reason why regular monitoring of CV risk factors is recommended for all patients with spondyloarthritis (including AS) (27). To what extent the current standard of care in the UK contributes to better control of classical CV risk factors in this population is unclear. There is insufficient data to make conclusion about the annual incidence rate (or similar metric) of acquiring a new risk CV factor among AS patients initiating tofacitinib, and how this would affect discontinuation rates. The results from the network meta-analyses versus adalimumab and secukinumab suggest no statistically significant differences. Please also refer to the data presented in section B.3.10 of the main submission and response to question A13.

A6. Please present baseline characteristics and key trial results (i.e., BASDAI 50, BASDAI change from baseline and BASFI change from baseline) for trials A3921120 and A3921119 (tofacitinib 5mg arms and placebo) which exclude the

at-risk patients (over 65s, current/past smokers, or those with cardiovascular or malignancy risk factors), to support the answer in A5 a).

These data have not been generated as current marketing authorisations are not limited to patients with no risk factors present. Pfizer also believes that the clinical effectiveness of tofacitinib in AS is unlikely to be significantly different between the at-risk and non-at-risk patients. Please note that these studies were not powered to detect difference between tofacitinib, and placebo based on risk factors.

A7. For study A3921120 please present tables comparing:

a) The baseline characteristics of the biologic-naïve subgroup with those of biologic-experienced subgroup (ideally using the revised trial cohort as per question A6).

Baseline characteristics are presented below for both biologic-naïve and biologic-experienced subgroup of patients from study A3921120.

Table 9 Demographic and Baseline Characteristics by Treatment Group and by Prior biologic use (biologic-naïve) study A3921120

	Tofacitinib 5 mg BID (N=[redacted])	Placebo -> Tofacitinib 5 mg BID (N=[redacted])	Total (N=[redacted])
Age (Years)			
Mean (Std.Dev.)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
Gender,n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race,n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m**2)			
Mean (Std.Dev.)	[redacted]	[redacted]	[redacted]
Smoking Status,n (%)			
Never Smoked	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]

Median disease duration since diagnosis, years	[redacted]	[redacted]	[redacted]
HLA-B27 positive (%)	[redacted]	[redacted]	[redacted]
BASFI mean (SD)	[redacted]	[redacted]	[redacted]
BASDAI mean (SD)	[redacted]	[redacted]	[redacted]
BASMI (Linear-Method), mean (SD)	[redacted]	[redacted]	[redacted]

Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational product. N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects in each analysis category (Percentages were based on N). Body Mass Index (kg/m**2) = weight (kg) / [height (cm)*0.01]**2. Height is at Screening and weight is at baseline. Baseline was defined as last non-missing assessment on or before day 1 and prior to first dose of investigational product. Prior treatment history (2 categories) was derived from clinical database.
Source: Study A3921120

Table 10: Demographic and Baseline Characteristics by Treatment Group and by Prior biologic use (biologic experienced) study A3921120

	Tofacitinib 5 mg BID ([redacted])	Placebo -> Tofacitinib 5 mg BID (N=[redacted])	Total (N=[redacted])
Age (Years)			
Mean (Std.Dev.)	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]
Gender,n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race,n (%)[b]			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m**2)			
Mean (Std.Dev.)	[redacted]	[redacted]	[redacted]
Smoking Status, n (%)			
Never Smoked	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]

Median disease duration since diagnosis, years	[redacted]	[redacted]	[redacted]
HLA-B27 positive (%)	[redacted]	[redacted]	[redacted]
BASFI mean (SD)	[redacted]	[redacted]	[redacted]
BASDAI mean (SD)	[redacted]	[redacted]	[redacted]
BASMI (Linear-Method), mean (SD)	[redacted]	[redacted]	[redacted]

Safety Analysis Set (SAFETY) - All subjects who were randomized and received at least one dose of the investigational product. N: Number of subjects included in the Safety Analysis Set; n (%): Number of subjects in each analysis category (Percentages were based on N). Body Mass Index (kg/m**2) = weight (kg) / [height (cm)*0.01]**2. Height is at Screening and weight is at baseline. Baseline was defined as last non-missing assessment on or before day 1 and prior to first dose of investigational product. Prior treatment history (2 categories) was derived from clinical database.
Source: Study A3921120

b) The results for biologic-naïve with biologic-experienced cohorts for the following outcomes (ideally using the revised trial cohort as per question A6): ASAS20, ASAS 40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline, BASMI change from baseline, total back pain, nocturnal spinal pain and ASQoL. For each trial arm, please present numerators and denominators for binary outcomes, or means for continuous outcomes. Please present results as risk ratios or mean differences, with 95% confidence intervals.

Please see Appendix 1 summarising the data for biologic naïve and biologic experienced cohorts for ASAS 20, ASAS 40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline, BASMI change from baseline and ASQoL.

Tofacitinib was consistently efficacious across pre-defined subgroups for both ASAS20 and ASAS40 response (Table 2; *table was adjusted with numerators and denominators as requested*).

Table 11. Pre-defined Subgroup Analysis of ASAS20 and ASAS40 Response Rates at Week 16 in A3921120 (Full Analysis Set)

	Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
	N	n	R (%)	N	n	R (%)	
ASAS20							
	102	63	61.8	105	35	33.3	[redacted]

	Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
	N	n	R (%)	N	n	R (%)	
bDMARD naïve							
TNFi-IR or bDMARD use [Non-IR	31	12	38.7	31	5	16.1	[redacted]
ASAS40							
bDMARD naïve; N=207	102	46	45.1	105	15	14.3	[redacted]
TNFi-IR or bDMARD use [Non-IR]; N=62	31	8	25.8	31	2	6.5	[redacted]

Source: (28, 29)

Abbreviations: TNFi-IR tumor necrosis factor inhibitor(s)-inadequate responder; ASAS, Assessment of Spondyloarthritis International Society; bDMARD- biological Disease-modifying antirheumatic drug; R, Response.

Results for total back pain and nocturnal spinal pain have now been added to Appendix 1.

The results of these analyses should be interpreted with caution as the study was not powered to detect difference in subgroups by prior biologic treatment.

b) The ASAS 40 subgroup results for all the pre-specified subgroups listed in Table 10 of the main company submission (ideally using the revised trial cohort as per question A6). Please present results as risk ratios with 95% confidence intervals.

Requested data for all analysed sub-groups, including pre-specified sub-groups, is presented below (Table 12). The study was not powered to detect difference between treatment arms in these subgroups. Risk ratios are currently not available for this data.

Table 12. ASAS40 Response Rate at Week 16 by pre-defined Subgroup.

Category		Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
		N	n	R (%)	N	n	R (%)	
Geographic Region	North America	16	[redacted]	[redacted]	11	[redacted]	[redacted]	[redacted]
	European Union	51	[redacted]	[redacted]	55	[redacted]	[redacted]	[redacted]

Category		Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
		N	n	R (%)	N	n	R (%)	
	Asia	23	[redacted]	[redacted]	30	[redacted]	[redacted]	[redacted]
	Rest of World	43	[redacted]	[redacted]	40	[redacted]	[redacted]	[redacted]
Gender	Male	116	[redacted]	[redacted]	108	[redacted]	[redacted]	[redacted]
	Female	17	[redacted]	[redacted]	28	[redacted]	[redacted]	[redacted]
Race	White	107	[redacted]	[redacted]	106	[redacted]	[redacted]	[redacted]
	Asian	25	[redacted]	[redacted]	30	[redacted]	[redacted]	[redacted]
	Other	1	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Age at baseline	<65 years	127	[redacted]	[redacted]	136	[redacted]	[redacted]	[redacted]
	≥65 years	6	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Baseline weight	<60	18	[redacted]	[redacted]	16	[redacted]	[redacted]	[redacted]
	≥60 - ≤100	97	[redacted]	[redacted]	110	[redacted]	[redacted]	[redacted]
	>100	18	[redacted]	[redacted]	10	[redacted]	[redacted]	[redacted]
Baseline Body Mass Index (BMI)	<25	50	[redacted]	[redacted]	59	[redacted]	[redacted]	[redacted]
	≥25 - <30	53	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]
	≥30 - <40	26	[redacted]	[redacted]	30	[redacted]	[redacted]	[redacted]
	≥40	3	[redacted]	[redacted]	3	[redacted]	[redacted]	[redacted]
	Missing	1	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
AS Disease Symptom Duration	<5 years	23	[redacted]	[redacted]	35	[redacted]	[redacted]	[redacted]
	≥ 5 years	110	[redacted]	[redacted]	101	[redacted]	[redacted]	[redacted]
Baseline AS Disease Activity	Inactive disease	1	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
	Low activity	2	[redacted]	[redacted]	1	[redacted]	[redacted]	[redacted]
	High activity	48	[redacted]	[redacted]	41	[redacted]	[redacted]	[redacted]
Baseline hsCRP	≤2.87 mg/L	23	[redacted]	[redacted]	20	[redacted]	[redacted]	[redacted]
	>2.87 mg/L	110	[redacted]	[redacted]	116	[redacted]	[redacted]	[redacted]

Category		Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
		N	n	R (%)	N	n	R (%)	
Baseline Smoking Status	Never	75	[redacted]	[redacted]	73	[redacted]	[redacted]	[redacted]
	Former	24	[redacted]	[redacted]	19	[redacted]	[redacted]	[redacted]
	Current	34	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]
Day 1 Concomitant csDMARD Use	Yes	29	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]
	No	104	[redacted]	[redacted]	92	[redacted]	[redacted]	[redacted]
HLA-B27	Negative	11	[redacted]	[redacted]	13	[redacted]	[redacted]	[redacted]
	Positive	107	[redacted]	[redacted]	115	[redacted]	[redacted]	[redacted]
	Missing	15	[redacted]	[redacted]	8	[redacted]	[redacted]	[redacted]

Source: (17)

A8. The NICE scope lists symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) as outcomes but results for these outcomes do not seem to be reported in the submission. Please report results for these outcomes, or explain why they were not evaluated in the tofacitinib trials.

Data on extra-articular manifestations from the clinical trial programme of tofacitinib in AS patients

In studies A3921110 and A3921120 patients with extra-articular manifestations (EAM) were not excluded. EAM outcomes were reported as safety events and were not part of the primary or secondary endpoints of the studies. Overall, EAM-related adverse events were low in the whole study population, including tofacitinib-treated patients. In general, prevalence of EAMs at baseline in A3921119 and A3921120 study populations was low compared to the general AS population. The frequency of EAMs at baseline and the number of treatment-emergent EAMs was insufficient to draw statistically significant conclusions on the effect of tofacitinib on EAMs in the AS clinical trial programme. Table 13 summarises the EAMs from phase 2 and phase 3 clinical trials of tofacitinib for the AS indication (24, 30).

Table 13. Extra-articular manifestations in clinical trials A3921119 and A3921120

		Uveitis	PsO	IBD

Study	Time of observation	Pbo	Tofa 5mg BID	Pbo	Tofa 5mg BID	Pbo	Tofa 5mg BID
Phase 2 1119 (N placebo BID=51 N Tof 5mg BID=52)	Medical h/o Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phase 3 1120 (N placebo BID→tofa 5mg BID =136 N Tof 5mg BID=133)	Medical h/o Baseline n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current diagnosis with medical h/o at baseline N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Up to Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Up to Week 48[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. One serious infection event of chronic iridocyclitis (uveitis); however, an infective process was not confirmed. This was considered to be a chronic event unrelated to study treatment and resolved following treatment with intravenous antibiotics and glucocorticoids; b.Includes all cases observed up to week 48. Note 131/136 patients on the placebo→tofacitinib treatment group were advanced to tofacitinib 5mg BID at week 16 ([redacted], none due to an adverse event related to uveitis, psoriasis or inflammatory bowel disease) ; c. Double-blinded phase of placebo vs tofacitinib lasted up to week 16 only; d. number of cases include those observed in the placebo→tofacitinib treatment group up to week 16.

Abbreviations: h/o, history of; BID, twice daily; Tofa, tofacitinib; PsO, psoriasis; Pbo, placebo; IBD, inflammatory bowel disease

Other data on extra-articular manifestations with the use of tofacitinib

The positive results on dermatological outcomes of tofacitinib in patients with psoriatic arthritis (PsA) have been previously reported in the clinical trial programme for this indication. A post-hoc analysis from phase 3 trials (OPAL Broaden-NCT01877668 and OPAL Beyond-NCT01882439) in patients with active PsA and inadequate response to csDMARDs or TNFi found that both tofacitinib 5mg BID and tofacitinib 10mg BID (the latter unlicenced in this indication) significantly improved dermatologic signs and symptoms and dermatology-related quality of life versus placebo at month 3 (31). Clinically meaningful improvements were observed up to 12 months for both tofacitinib doses. Of note, the presence of active plaque psoriasis at screening was a key inclusion criterion for both OPAL Broaden and OPAL Beyond studies. Results for dermatological outcomes in this analysis were similar to those observed in adalimumab-treated patients within the study population.

Tofacitinib is licensed in the UK for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. The recommended dose is 10mg BID for induction therapy, followed by 5mg BID in maintenance therapy. A summary of the clinical efficacy data for this indication can be found as part of the summary of product characteristics of tofacitinib (12).

Data on tofacitinib clinical efficacy in uveitis from the clinical trial program across all the several indications is very limited, due to study design, inclusion criteria and baseline characteristics of the different study populations, which would not allow the performance of a post-hoc analysis for outcomes related to inflammatory ocular disease. A few case reports have been published on the positive effect of tofacitinib in adult patients with uveitis in the setting of juvenile idiopathic arthritis (32, 33).

In conclusion, patients with ankylosing spondylitis with active history of PsA with skin involvement and/or inflammatory bowel disease could potentially benefit additionally from tofacitinib treatment. The efficacy data on uveitis is insufficient to recommend tofacitinib use in patients with active uveitis.

A9. For the placebo and tofacitinib 5mg arms in trials A3921119 and A3921120 please present data on the numbers of patients with concomitant NSAID use, concomitant corticosteroid use, and concomitant csDMARDs use (i.e., three separate outcomes) at weeks 0, 2, 4, 8, 12 and 16.

Data for currently available timepoints (baseline for study A3921119 and Weeks 0,16 and 48 for study A3921120) are presented below (Table , Table). As per the study protocol of A3921120, subjects receiving permitted concomitant csDMARDs, NSAIDs, selective COX-2 inhibitors, and/or corticosteroids must have remained on the same dose regimen throughout the study.

Table 14. Concomitant Medications for Ankylosing Spondylitis by Medication Type and Treatment Group taken at baseline in A3921119 trial.

Medication type	Baseline	
	Tofacitinib 5 mg BID N=52	Placebo N=51
Subjects with any Concomitant NSAID, n (%)	[redacted]	[redacted]

Subjects with any Corticosteroid, n (%)	[redacted]	[redacted]
Subjects with any DMARD, n (%)	[redacted]	[redacted]

Source: (16)

Table 15. Concomitant Medications for Ankylosing Spondylitis by Medication Type and Treatment Group taken at baseline, week 16 and week 48 in A3921120 trial.

Medication type	Baseline		Up to week 16		Up to week 48	
	Tofacitinib 5 mg BID N=133	Placebo → Tofa 5mg BiD N=136	Tofacitinib 5 mg BID N=133	Placebo → Tofa 5mg BiD N=136	Tofacitinib 5 mg BID N=133	Placebo → Tofa 5mg BiD N=136
Subjects with Any Concomitant NSAID, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with Any Oral Corticosteroid, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with Any Intra-Articular Corticosteroid, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with Any csDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: (17, 34)

A10. PRIORITY QUESTION: Clinical trial evidence is available for two alternative JAK inhibitors, upadacitinib and filgotinib, in this same indication. Please comment on the plausibility of a common effect or of a class effect on i) the effectiveness and ii) safety, across all these agents, which could make evidence on these alternative drugs relevant to the current appraisal. Note that, on safety, the FDA has issued a warning on all JAKs based solely on evidence on tofacitinib, explicitly considering the evidence exchangeable across treatments.(35)

Upadacitinib and filgotinib were not part of the final scope and therefore not included in the decision problem of this appraisal. Therefore, they were not included in the analyses of the submission. Upadacitinib has a marketing authorisation for ankylosing spondylitis, however it is not currently recommended in UK clinical practice as it is going through NICE technology appraisal in parallel with tofacitinib.

Filgotinib is not currently recommended for AS and there is no information that a technology appraisal is being conducted for this indication for filgotinib on the NICE website either.

There is very limited data available in the public domain in terms of clinical effectiveness of upadacitinib in AS and no head-to-head or indirect treatment comparison has been published. Therefore, Pfizer cannot comment on the effectiveness of these treatments in AS or the relative effectiveness compared with tofacitinib.

It is important to consider that among JAKis, a study like ORAL Surveillance (CV risk-enriched, head-to-head, event-driven, long-term) has only been conducted with tofacitinib to date.

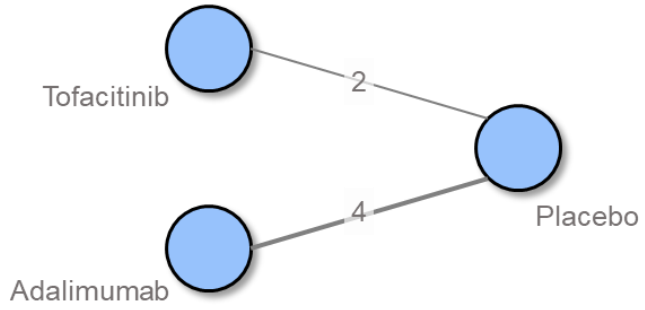
Indirect and mixed treatment comparisons – methods

A11. PRIORITY QUESTION: Network meta-analyses (indirect comparisons only) were conducted to compare tofacitinib to adalimumab via Placebo. However, few details are provided on the methods used and the analyses cannot be fully checked or reproduced. Please provide a full NMA report including:

a) ***Full details of the NMA feasibility assessment including the assessment of baseline characteristics of included studies with reference to potential effect modifiers, network connectivity and other relevant points – see Cope et al (2014).(36)***

Please find study and patient characteristics for the 6 included RCTs provided in Appendix 2 Table_of_trial_char-ADA-NMA.xlsx. A network diagram for this NMA is provided in Figure 13.

Figure 13: Network Diagram of Adalimumab and Tofacitinib



b) Full details of the BUGS code, full data and initial values used for each model (fixed/random effects with and without baseline risk adjustment) and for each outcome (efficacy, quality of life and discontinuation/adverse events). These should be provided as electronic files, with data and initial values in BUGS format, to allow all analyses to be reproduced.

These files are provided within the zip folder in Appendix 3 - NICE AS NMA for ERG.zip

c) Full details of the number of iterations used for burn-in and to obtain the posterior samples, including any considerations on convergence and autocorrelation that were taken into account, for each model (fixed/random effects with and without baseline risk adjustment) and outcome (efficacy, quality of life and discontinuation/adverse events).

A burn-in of 10,000 and 90,000 posterior samples were used to estimate all outcomes except the RE ASAS 20 outcome, which used 77,649 samples due to computational memory limitations at the time of execution. No concerns about convergence were identified.

d) Full model fit statistics including the posterior mean of the residual deviance and pD (the effective number of parameters). The posterior mean of the residual deviance should be compared to the number of independent data points in each NMA to assess whether the model fits

the data well. It would be helpful if these values were added to Table 19 and other similar tables in Appendix D.

These results are provided in the Excel workbooks Appendix 3, under Binary AS NMA results for ERG.xlsm and Continuous NMA results for ERG.xlsm.

e) The posterior density and posterior median and 95%CrI for the between-study standard deviation (τ), not the variance (τ2), for all random effects models. If possible, the plot of the posterior density for τ should be combined with the prior distribution in the same plot to show how the data has updated the prior information. It would be helpful if these values were added to Table 19 and other similar tables in Appendix D. See also question A15 on different models for heterogeneity.

The between-study standard deviation for all RE models are provided in the Excel workbooks Appendix 3. A plot of these posteriors was not possible to create.

f) Posterior summaries (median and 95% CrI, as a minimum) for the regression coefficient(s) for the baseline risk adjusted NMAs.

These outcomes are provided in the Excel workbooks Appendix 3.

g) The 95%CrI for the ranks.

These outcomes are provided in the Excel workbooks Appendix 3.

A12. Previous appraisals of biologic drugs in this disease area have explored the inclusion of class effects across treatments in the NMA, see for example the MTA HTA report [TA383].

a) Please include a class-effect for anti-TNFs in all the NMAs. Alternative model specifications should be evaluated using model fit statistics. The relevant treatment effect estimates should be compared across models. In particular, the relative effect of tofacitinib should be compared to the pooled class effect of anti-TNFs, as well as to the shrunken effect of adalimumab (or revised comparator) form the class model.

b) Please provide a full report of these analyses, including all data and code as specified in clarification question A11, including not only

shrunken estimates for the particular treatments of interest but also estimates of the predictive distribution of the class-effect(s), as was done in the MTA [TA383].

c) ***Please provide details and justification for all prior distributions used, including the justification for the prior distributions used for the between-study heterogeneity in random effects models (see also question A15) and for the regression coefficient(s) in baseline risk adjusted models (see also question A18).***

d) ***Please comment on the treatment effect estimates for tofacitinib compared to the predictive class effect for TNF inhibitors, in biologic-naïve and biologic-experienced patients.***

The NMA presented in the main submission included only tofacitinib and adalimumab, so assuming a class effect for all anti-TNFs was not possible to include in the framework. However, it is not expected that the analysis would lead to different conclusions about the clinical effectiveness of tofacitinib versus adalimumab, as it has been previously established (in NICE TA383 and TA407) that the clinical effectiveness across TNF inhibitors is equivalent. Besides, the evidence available for TNF inhibitors contained placebo-controlled trials only, there were no loops in the network; therefore introducing studies for other TNFs is not expected to lead to different conclusion and the number of studies available for each comparators would stay the same (4 studies for adalimumab and 2 studies for tofacitinib).

A13. PRIORITY QUESTION: Clinical expert advice to the ERG is that most patients will not receive tofacitinib as a first-line DMARD. Please therefore conduct and present NMAs which compare tofacitinib in biologic-experienced patients with treatments often used at later lines of therapy, e.g., IL-17s (see also questions A5, A10).

Pfizer considers that adalimumab is the most relevant comparator, irrespective of line of therapy because it is the most prescribed bDMARD in AS, has demonstrated similar health benefits to other TNFis and IL-17is in previous NICE appraisals and is likely to have the cheapest net price, as biosimilar versions are available in the UK. We would like to highlight that rechallenging with an anti-TNF is also common in this

disease area, therefore adalimumab is still a relevant comparator even for later lines of therapy. It was also concluded in the secukinumab appraisal (TA407) that the clinical effectiveness is similar between the two technologies. However, for completeness and in order to remove the uncertainty around the use of tofacitinib in subsequent line of therapy, we present results for NMAs which compare tofacitinib in biologic-naïve patients with secukinumab are presented below. As expected, the results show that tofacitinib has similar clinical effectiveness to secukinumab in biologic-naïve patients with AS. In addition, the results for biologic-experienced patients with treatments often used at later lines of therapy are presented below, which show that tofacitinib has similar clinical effectiveness to secukinumab and ixekizumab in biologic-experienced population in all relevant endpoints.

Studies included in the NMAs versus IL-17s are listed in Table 16 below.

Table 16. Studies Included in NMAs

Study	Comparator Arms	Double-Blind Period
A39211191 (30)	Tofacitinib 5mg BID	12 weeks
A39211202 (17)	Tofacitinib 5mg BID	16 weeks
MEASURE 2 (37, 38)	Secukinumab 150mg (weeks 0, 1, 2, 3, 4 and Q4W thereafter) (L)	16 weeks
MEASURE 4 (39)	Secukinumab 150mg (NL) (weeks 0, 1, 2, 3, 4 and Q4W thereafter) Secukinumab 150mg (L) (weeks 0, 1, 2, 3, 4 and Q4Wthereafter) + loading dose	16 weeks
MEASURE 5 (40)	Secukinumab 150mg (L) (weeks 0, 1, 2, 3, 4 and Q4Wthereafter) + loading dose	16 weeks
COAST-W(41)	Ixekizumab 80 mg Q4W	16 weeks

Key: BID, twice daily; Q4W, every 4 weeks; L, loading dose; NL, no loading dose

Summary of Statistical Methods

The analysis, similar to the NMA versus adalimumab, was conducted from a Bayesian perspective using WinBUGS. Vague prior distributions were assumed. Convergence was assessed by running 3 chains using the Gelman Rubin Statistic. Both fixed and random effect models were fit and goodness of fit was determined using the deviance information criterion (DIC). Where feasible, baseline-risk adjusted

fixed and random effects were also performed. WinBUGS codes from NICE TSD 2 and 3 were adapted to conduct the analysis within WinBUGS.

The analysis was conducted from a Bayesian perspective using WinBUGS. Non-informative prior distributions were assumed. Odds ratios (OR) and ln(OR) values were calculated to assess the treatment effect. A burn-in of 10,000 iterations and another 30,000 iterations were used for inferences, unless where otherwise noted. Convergence was assessed by running 3 chains using the Brooks-Gelman-Rubin (BGR) Statistic. Both fixed and random effect models were fit and goodness of fit was determined using the deviance information criterion (DIC). Overall heterogeneity in studies included in the network was assessed using the τ2. Between-study heterogeneity for each comparison was assessed using Cochrane's Q and the I2. Tests for inconsistency were conducted using an unrelated mean effects (UME) inconsistency model for networks that contained independent loops. Heterogeneous comparisons were generally consistent across multiple outcomes. Therefore, no sensitivity analyses were conducted by excluding studies contributing to heterogeneity.

ASAS20 Results: Biologic-naive

Network for ASAS20

A total of three studies for secukinumab were included in the network for ASAS20, as depicted in Figure 14 Response rates for ASAS20 by study and study arm are provided in Table 17.

Figure 14: Network for Tofacitinib and Secukinumab

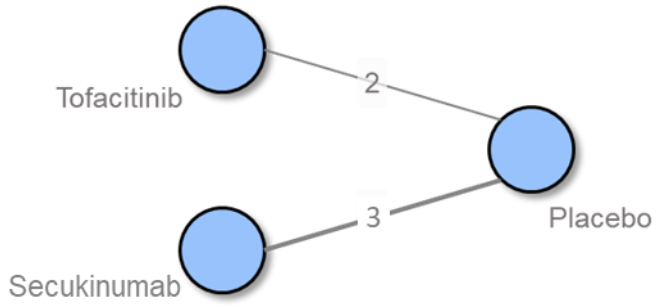


Table 17: Proportion of Patients with ASAS20 Response Among Study Arms

Study Name	Intervention	N	R (%)
A3921119(30)	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
A3921120[a,](17)	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
MEASURE 2[a,](37, 38)	Secukinumab (L)	44	30 (68.2)
	Placebo	45	14 (31.1)
MEASURE 4[a,](39)	Secukinumab (L)	85	51 (60.0)
	Secukinumab (NL)	85	53 (62.4)
	Placebo	83	41 (49.4)
MEASURE 5[a,(40)]	Placebo	122	45 (36.9)
	Secukinumab (L)	240	140 (58.3)

Key: L, loading dose; N, total denominator; NL, no loading dose; R, total numerator;

a. Results from the subgroup for bDMARD/TNFi-naïve patients were used

Model Fit and Heterogeneity

Given a similar DIC between the fixed and random effects models ([redacted]) and a low degree of heterogeneity overall, the simpler fixed effects model was favored without baseline risk adjustment was preferred.

Table 18: Model Fit Statistics for ASAS20 Fixed and Random Effects Models Without and With Baseline Risk Adjustment

	Without Baseline Risk Adjustment		With Baseline Risk Adjustment	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Between-study variance (τ^2)	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: DIC, deviance information criterion

The I^2 values for comparisons vs placebo were high for a number of comparisons, indicating evidence for some heterogeneity between studies (Table 17). A moderate degree of heterogeneity was observed for the secukinumab (loading) vs. placebo

between the MEASURE 2, and MEASURE 5 studies and in studies comparing adalimumab vs. placebo.

Table 19: Heterogeneity Statistics for ASAS20 Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]
Tofacitinib vs placebo	A3921119(30), A3921120(17)	[redacted]	[redacted]

Key: L, loading dose

The inconsistency model had a [redacted] and was higher compared to the fixed effects model. Comparisons of direct and indirect estimates and the p-value between the differences does not suggest inconsistency. Other loops consisted of 3-arm trials in combination with 2-arm trials and are therefore best interpreted in the context of heterogeneity between studies.

Results for ASAS20 Response

Odds ratios for the fixed and random effects models are shown in Table 18.

[redacted]

Table 20: Fixed Effects and Random Effects Models for ASAS20 Without Baseline Risk Adjustment

	Fixed Effects		Random Effects	
	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; OR, odds ratio; PBO, placebo
TOF, tofacitinib; TX, treatment
a. ORs greater than 1 favor the treatment; b. ORs greater than 1 favor tofacitinib.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment.

Table 21: Fixed Effects and Random Effects Models for ASAS20 with Baseline Risk Adjustment

	Fixed Effects		Random Effects	
	TX vs PBO	TOF vs TX	TX vs PBO	TOF vs TX

	OR (95% CrI)[a]	OR (95% CrI)[b]	OR (95% CrI)[a]	OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; FE, fixed effects; OR, odds ratio; PBO, placebo; RE, random effects; TOF, tofacitinib; TX, treatment
a. ORs greater than 1 favor the treatment; b. ORs greater than 1 favor tofacitinib.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment

All pairwise comparisons are depicted below.

[redacted] (Table 22).

Table 22. League Table for ASAS20 (Fixed Effects Model Without Baseline Risk Adjustment)

	TOF			
SEC(L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PBO, placebo
Green indicates where comparisons are considered to be significant.

Table 23. League Table for ASAS20 (Fixed Effects Model with Baseline Risk Adjustment)

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PBO, placebo
Green indicates where comparisons are considered to be significant.

Table 24. SUCRA Rankings for ASAS20

Fixed Effects Without Baseline Risk Adjustment			Fixed Effects With Baseline Risk Adjustment		
Rank	Treatment	SUCRA	Rank	Treatment	SUCRA
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; L, loading dose; NL, no loading dose

ASAS20 Results: Biologic Experienced

Network for ASAS20 Response: Biologic Experienced

The network diagram for ASAS20 response among biologic experienced patients is shown in Figure 15. Only the A3921120, MEASURE 2, MEASURE 4 and COAST-W studies provided ASAS20 data on patients in the biologic experienced patient population. Results were provided in the form of subgroup analyses for A3921120, MEASURE 2, MEASURE 4 and MEASURE 5. The COAST-W study was conducted solely on the TNFi-IR patient population. A summary of the ASAS20 response rates in this patient population is provided in Table .

Figure 15: Network Diagram for ASAS20 Response: Biologic Experienced

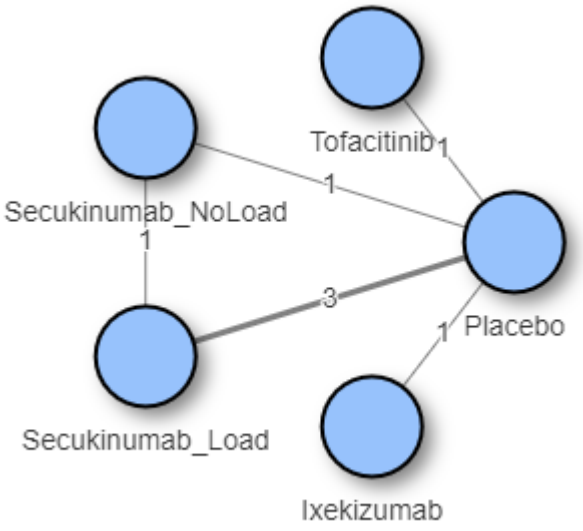


Table 25: Proportion of Patients ASAS20 Response Among Study Arms: Biologic Experienced

Study Name	Intervention	N	R (%)
A3921120(17)	Placebo	[redacted]	[redacted]
	Tofacitinib	[redacted]	[redacted]
COAST-W(41)	Placebo	104	31 (29.8)
	Ixekizumab	114	55 (75.0)
MEASURE 2(42)	Placebo	29	7 (24.1)
	Secukinumab (L)	28	14 (50.0)
MEASURE 4(39)	Placebo	34	14 (41.2)
	Secukinumab (L)	31	18 (58.1)
	Secukinumab (NL)	32	19 (59.4)

MEASURE 5(40)	Placebo	31	11 (35.5)
	Secukinumab (L)	65	38 (58.5)

Key: NL, no loading dose; L, with loading dose

Model Fit and Heterogeneity

Model fit statistics are provided in Table . Little heterogeneity was observed in the model as demonstrated by a low I^2 of 0.0% (Q, 0.8 [p-value = 0.7788) in secukinumab comparisons in MEASURE 2, MEASURE 3 and MEASURE 4. Given the paucity of studies, and low evidence of heterogeneity, only the fixed effects model without baseline risk adjustment was fit.

Table 26: Model Fit Statistics for ASAS20 Fixed Effects Models Without Baseline Risk Adjustment: Biologic Experienced

	Fixed Effects
Between-study variance (τ^2)	[redacted]
DIC	[redacted]

Key: DIC, deviance information criterion

Results for ASAS20 Response: Biologic Experienced

Results for all possible pairwise comparisons are shown below.

[redacted]

Table 27: Fixed Effects Model for ASAS20: Biologic Experienced

	Fixed Effects Model	
	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: FE, fixed effects; RE, random effects; DIC, deviance information criterion; TX, treatment; TOF, tofacitinib; OR, odds ratio; PBO, placebo

a. ORs greater than 1 favor the treatment; b. ORs greater than 1 favor tofacitinib

Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment.

Table 28: League Table for ASAS20: Biologic Experienced

	TOF				
SEC (L)	[redacted]	SEC (L)	--	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--	--
IXE	[redacted]	[redacted]	[redacted]	IXE	--
PCB	[redacted]	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; IXE, ixekizumab; PBO, placebo

Green indicates where comparisons are considered to be significant.

Table 29: SUCRA ranking for ASAS20: Biologic Experienced

Rank	Treatment	SUCRA
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; L, loading dose; NL, no loading dose

ASAS40 Results: Biologic-Naïve

Network for ASAS40 Response

A total of 5 studies were included in the network for ASAS40 response. Response rates for ASAS40 by study and study arm are provided in Table 28**Table** .

Figure 16: Network for Tofacitinib and Secukinumab

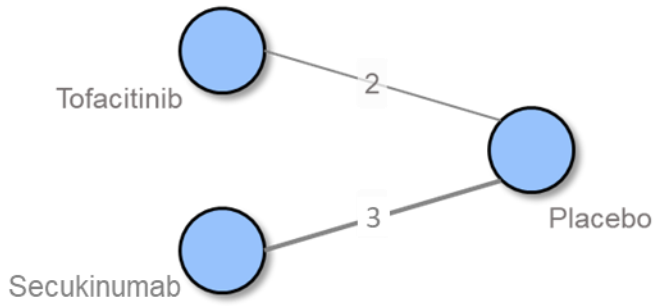


Table 30. Proportion of Patients with ASAS40 Response Among Study Arms

Study Name	Intervention	N	R (%)

A3921119(30)	Placebo	[redacted]	[redacted]
	Tofacitinib	[redacted]	[redacted]
A3921120[a,(17)]	Placebo	[redacted]	[redacted]
	Tofacitinib	[redacted]	[redacted]
MEASURE 2[a,](37, 38)	Secukinumab (L)	44	19 (43.2)
	Placebo	45	8 (17.8)
MEASURE 4[a,](39)	Secukinumab (L)	85	34 (40)
	Secukinumab (NL)	85	33 (38.8)
	Placebo	83	25 (30.1)
MEASURE 5[a,(40)]	Secukinumab (L)	240	102 (42.5)
	Placebo	121	22 (18.0)
	Bimekizumab 320 mg	61	28 (45.9)
	Placebo	60	8 (13.3)

a. Results from the subgroup for bDMARD/TNFi-naïve patients were used.

Model Fit and Heterogeneity

Model fit statistics for both the fixed and random effects models are shown in Table 29**Table** . Given a similar DIC between the fixed and random effects models (Difference < 3), the simpler fixed effects model was favoured. The between study variance for both models may suggest moderate heterogeneity, though the random effects model does not provide an improved fit. Results from baseline-adjusted models did not vary substantially from models without baseline risk adjustment.

Table 31. Model Fit Statistics for ASAS40 Fixed and Random Effects Models Without and With Baseline Risk Adjustment

	Without Baseline Risk Adjustment		With Baseline Risk Adjustment	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Between-study variance (τ^2)	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: DIC, deviance information criterion

A moderate degree of heterogeneity was observed for comparisons of secukinumab (with loading dose) vs. placebo (Table 32).

Table 32: Heterogeneity Statistics for ASAS40 Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]
Tofacitinib vs placebo	A3921119(30), A3921120(17)	[redacted]	[redacted]

Key: L, loading dose

Results for ASAS40 Response

Odds ratios for the fixed and random effects models are shown below. Results were generally similar between the fixed and random effects models. Comparisons for tofacitinib vs. secukinumab were not significant (ie, all 95% credible intervals contain or cross value of 1).

Table 33: Fixed Effects and Random Effects Models for ASAS40 Without Baseline Risk Adjustment

	Fixed Effects		Random Effets	
	FE (DIC =282.736)		**RE (DIC = 282.983)**	
	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: FE, fixed effects; RE, random effects; DIC, deviance information criterion; TX, treatment; TOF, tofacitinib; OR, odds ratio; PBO, placebo; NL, no loading dose; L, with loading dose
a. ORs greater than 1 favor the treatment.
b. ORs greater than 1 favor tofacitinib.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment.

Table 34: Fixed Effects and Random Effects Models for ASAS40 with Baseline Risk Adjustment

	Fixed Effects		**Random Effects**	
	TX vs PBO	TOF vs TX	TX vs PBO	TOF vs TX

	OR (95% CrI)[a]	OR (95% CrI)[b]	OR (95% CrI)[a]	OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: FE, fixed effects; RE, random effects; DIC, deviance information criterion; TX, treatment; TOF, tofacitinib; OR, odds ratio; PBO, placebo; NL, no loading dose; L, with loading dose
a. ORs greater than 1 favor the treatment.
b. ORs greater than 1 favor tofacitinib.
Green indicates where treatment is superior to the alternative treatment.

SUCRA rankings are provided in **Table** and the league table for all possible pairwise comparisons is shown in Table 35Table and Table 36.

Table 35. League Table for ASAS40 Response (Fixed Effects without Baseline Risk Adjustment)

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PBO, placebo

Green indicates where comparisons are considered to be significant.

Table 36. League Table for ASAS40 Response (Fixed Effects with Baseline Risk Adjustment)

	TOF			
Secukinumab (L)	[redacted]	SEC (L)	--	--
Secukinumab (NL)	[redacted]	[redacted]	SEC (NL)	--
Placebo	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PBO, placebo

Green indicates where comparisons are considered to be significant.

Table 37. SUCRA Rankings for ASAS40

Fixed Effects without Baseline Risk Adjustment			Fixed Effects with Baseline Risk Adjustment		
Rank	Treatment	SUCRA	Rank	Treatment	SUCRA
[redacted]					

Key: SUCRA, surface under the cumulative ranking curve; L, loading dose; NL, no loading dose

ASAS40 Results: Biologic Experienced

Network for ASAS40 Response: Biologic Experienced

The network diagram for ASAS40 response among biologic experienced patients is shown in Figure 17. Only the A3921120, MEASURE 2, MEASURE 4, and COAST-W studies provided ASAS40 data on patients with the biologic experienced patient population. Results were provided in the form of subgroup analyses for A3921120, MEASURE 2, MEASURE 4, AND MEASURE 5. The COAST-W study was conducted solely on the biologic experienced patient population. A summary of the ASAS40 response rates in this patient population is provided in Table 36**Table** .

Figure 17. Network Diagram for ASAS40 Response: Biologic Experienced

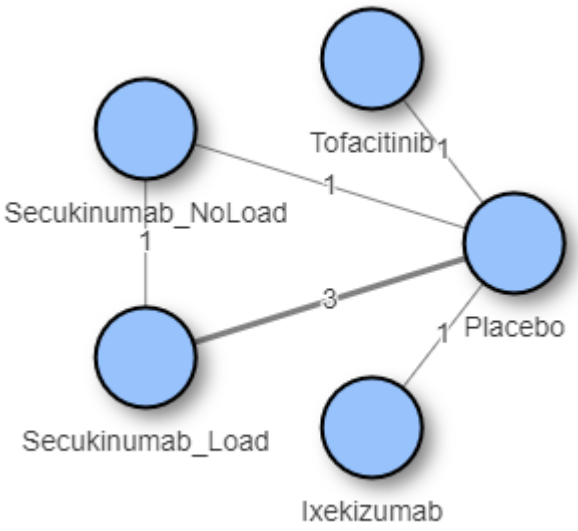


Table 38: Proportion of Patients ASAS40 Response Among Study Arms: Biologic Experienced

Study Name	Intervention	N	R (%)
A3921120(17)	Placebo	[redacted]	[redacted]
	Tofacitinib	[redacted]	[redacted]
COAST-W(41)	Placebo	104	13 (12.5)
	Ixekizumab	114	29 (25.4)
MEASURE 2(42)	Placebo	29	0 (0.0)
	Secukinumab (L)	28	7 (25)
MEASURE 4(39)	Placebo	34	8 (23.5)
	Secukinumab (L)	31	11 (35.5)
	Secukinumab (NL)	32	9 (28.1)
MEASURE 5(40)	Placebo	31	4 (12.9)
	Secukinumab (L)	65	32 (49.2)

Key: N, total denominator; R, total numerator; NL, no loading dose; L, with loading dose

Model Fit and Heterogeneity

Due to the paucity of studies and comparisons available, only fixed and random effects models without baseline risk adjustment were fit for the ASAS40 network in the biologic experienced population. Model fit statistics did not suggest a substantially better fit with the random effects mode and therefore the fixed effects model was preferred.

Table 39: Model Fit Statistics for ASAS40 Fixed and Random Effects Models Without Baseline Risk Adjustment: Biologic Experienced

	Without Baseline Risk Adjustment	
	Fixed Effects	Random Effects
Between-study variance (τ^2)	[redacted]	[redacted]
DIC	[redacted]	[redacted]

Key: DIC, deviance information criterion

Table 40: Heterogeneity Statistics for ASAS40 Comparisons: Biologic Experienced

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]

Key: L, loading dose

Results for ASAS40 Response: Biologic Experienced

Results for each treatment vs. placebo and tofacitinib vs. each treatment and for all possible pairwise comparisons are shown below.

[redacted]

Table 41: Fixed Effects Model for ASAS40: Biologic Experienced

	Fixed Effects Model	
	TX vs PBO OR (95% CrI)[a]	TOF vs TX OR (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: CrI, credible interval; L, loading dose; NL, no loading dose; TX, treatment; TOF, tofacitinib; OR, odds ratio; PBO, placebo
a. ORs greater than 1 favor the treatment; b. ORs greater than 1 favor tofacitinib.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment.

Table 42: League Table for ASAS40: Biologic Experienced

	TOF				
SEC (L)	[redacted]	SEC (L)	--	--	--

SEC (NL)	[redacted]	[redacted]	SEC (NL)	--	--
IXE	[redacted]	[redacted]	[redacted]	IXE	--
PCB	[redacted]	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; IXE, ixekizumab; PBO, placebo
Green indicates where comparisons are considered to be significant.

Table 43: SUCRA ranking for ASAS40: Biologic Experienced (Fixed Effects Model without Baseline Risk Adjustment)

Rank	Treatment	SUCRA
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve

BASDAI50 Results: Biologic-Naïve

No NMA of BASDAI50 outcomes tofacitinib and secukinumab could be conducted in biologic-naïve patients as BASDAI50 was not reported in the MEASURE studies.

BASDAI50 Results: Biologic Experienced

Network for BASDAI50 Response: Biologic Experienced

A total of 2 studies (A3921120 and COAST-W) with a total of 3 unique treatments (including placebo) were included in the network for BADSAI50 response. Response rates for BASDAI50 response by study and study arm are provided in Table 44.

Table 44: Proportion of Patients with BASDAI50 Response Among Study Arms: Biologic Experienced

Study Name	Intervention	N	R (%)
A3921120[a,](17)	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
COAST-W	Ixekizumab	28	25 (21.9)
	Placebo	93	10 (10.8)

Key: N, total denominator; R, total numerator
a. Results from the subgroup for Biologic Experienced patients were used.

Model Fit and Heterogeneity

The [redacted]. Random effects models were not fit due to the sparse network.

Results for BASDAI50 Response

Odds ratios for the fixed and random effects models are shown in Table 45. The

[redacted]

Table 45: Fixed Effects Models for BASDAI50: Biologic Experienced

	Fixed Effects Model	
	Tx vs PBO OR (95% CrI)[a]	Tof vs Tx OR (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]
Tofacitinib	[redacted]	

Key: CrI, credible interval; FE, fixed effects; RE, random effects; Tx, treatment; Tof, tofacitinib; OR, odds ratio; PBO, placebo; NL, no loading dose; L, loading dose
a. ORs greater than 1 favor the treatment
b. ORs greater than 1 favor tofacitinib
Green indicates where treatment is superior to the alternative treatment

BASDAI (Continuous) Results: Biologic-Naïve

Network for BASDAI (Continuous)

A total of 5 studies were included in the network for BASDAI (Table 46).

Figure 18: Network for Tofacitinib and Secukinumab

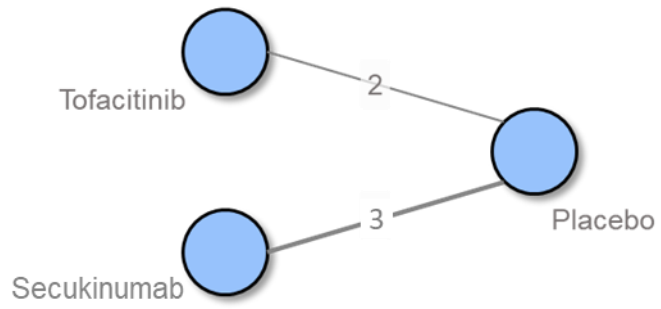


Table 46. Change from Baseline in BASDAI (Continuous) Among Study Arms

Study Name	Intervention	N	Change from Baseline (SE)
A3921119(30)	Tofacitinib	[redacted]	[redacted]

	Placebo	[redacted]	[redacted]
A3921120(17)	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
MEASURE 2[a,](37, 38)	Secukinumab (L)	85	-2.0 (0.30)
	Placebo	83	-1.2 (0.30)
MEASURE 4[a,](39)	Secukinumab (L)	85	-2.5 (0.23)
	Secukinumab (NL)	65	-2.7 (0.23)
	Placebo	57	-2.0 (0.23)
MEASURE 5[a,(40)]	Secukinumab (L)	20	-2.7 (0.15)
	Placebo	20	-1.5 (0.21)

Key: SE: standard error; L, loading dose; NL, no loading dose
a. Sulfasalazine is treated as placebo in the NMA.

Model Fit and Heterogeneity

Model fit statistics did not suggest an improved model fit with a random effects model (Table 47) and therefore the fixed effects model was preferred. Some heterogeneity was observed in secukinumab (with loading dose) comparisons (I^2 = 28.4%).

Table 47. Model Fit Statistics for BASDAI (Continuous) Fixed and Random Effects Models Without and With Baseline Risk Adjustment

	Without Baseline Risk Adjustment		With Baseline Risk Adjustment	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Between-study variance (τ^2)		[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: DIC, deviance information criterion

Table 48: Heterogeneity Statistics for BASDAI (Continuous) Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]
Tofacitinib vs Placebo	A3921119(30), A3921120(17)	[redacted]	[redacted]

Key: L, loading dose

Results for BASDAI (Continuous)

Results for fixed and random effects models across models are shown below.

[redacted]

[redacted].

Table 49: Fixed Effects and Random Effects Models for BASDAI (Continuous) Without Baseline Risk Adjustment

	Fixed Effects		Random Effects	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; DIC, deviance information criterion; Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where treatment is inferior to the alternative treatment.

Table 50: Fixed Effects and Random Effects Models for BASDAI (Continuous) with Baseline Risk Adjustment

	Fixed Effects		Random Effects	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; FE, fixed effects; RE, random effects; DIC, deviance information criterion; Tx, treatment; Tof, tofacitinib Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment. Pink indicates where treatment is inferior to the alternative treatment.

Table 51. League Table for BASDAI (Continuous): Fixed Effects without Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--

PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PBO, placebo
Green indicates where comparisons are considered to be significant.

Table 52. SUCRA Rankings for BASDAI (Fixed Effects)

Rank	Treatment	SUCRA
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dose

BASDAI (Continuous) Results: Biologic Experienced

Network for BASDAI (Continuous)

A total of 5 studies across 5 unique treatments (including placebo) were included in the network for BASDAI (Table 53).

Figure 19: Network for BASDAI Change from Baseline: Biologic Experienced

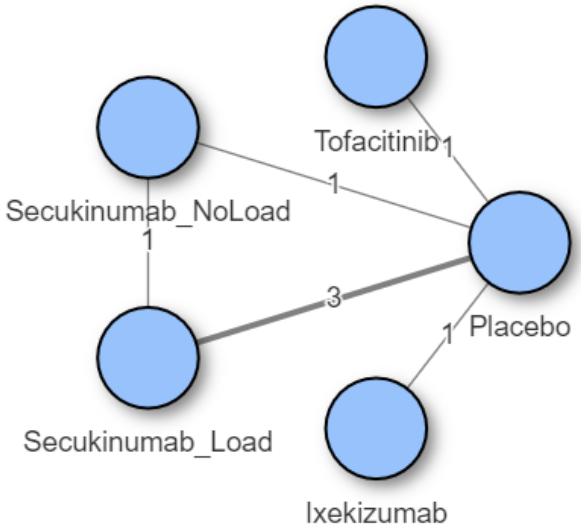


Table 53: Change from Baseline in BASDAI (Continuous) Among Study Arms: Biologic Experienced

Study Name	Intervention	N	Change from Baseline (SE)
A3921120	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]

COAST-W	Ixekizumab	114	-2.2 (0.20)
	Placebo	104	-0.9 (0.20)
MEASURE 2	Secukinumab (L)	22	-1.6 (0.40)
	Placebo	24	-0.6 (0.40)
MEASURE 4	Secukinumab (L)	31	-2.1 (0.42)
	Secukinumab (NL)	32	-2.4 (0.42)
	Placebo	34	-1.6 (0.40
MEASURE 5	Secukinumab (L)	65	-3.3 (0.3)
	Placebo	31	-1.7 (0.41)

Key: SE: standard error; L, loading dose; NL, no loading dose

Model Fit and Heterogeneity

Model fit statistics did not suggest an improved model fit with a random effects model selected (Table 52) and therefore the fixed effects model was preferred. Overall, studies in the network did not suggest a significant amount of heterogeneity based on τ^2. Because of the low heterogeneity no baseline risk adjustment was performed.

Table 54: Model Fit Statistics for BASDAI (Continuous) Fixed and Random Effects Models Without Baseline Risk Adjustment: Biologic Experienced

	Without Baseline Risk Adjustment	
	Fixed Effects	**Random Effects**
Between-study variance (τ^2)		[redacted]
DIC	[redacted]	[redacted]

Key: DIC, deviance information criterion

Table 55: Heterogeneity Statistics for BASDAI (Continuous) Comparisons: Biologic Experienced

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]

Key: L, loading dose

Results for BASDAI (Continuous)

Results for BASDAI are shown below.

[redacted]

Table 56: Fixed Effects and Random Effects Models for BASDAI (Continuous) without Baseline Risk Adjustment: Biologic Experienced

	Fixed Effects	Random Effects

	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; FE, fixed effects; RE, random effects; DIC, deviance information criterion; Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment.

Table 57: League Table for BASDAI (Continuous) Fixed Effects Without Baseline Risk Adjustment: Biologic Experienced

	TOF				
SEC (L)	[redacted]	SEC (L)	--	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--	--
IXE	[redacted]	[redacted]	[redacted]	IXE	--
PCB	[redacted]	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; NETA, netakimab; BIM 320, bimekizumab 320 mg; BIM 160, bimekizumab 160 mg; UPA, upadacitinib; FIL, filgotinib; CER 400, certolizumab 400 mg; CER 200, certolizumab 200 mg; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; IXE, ixekizumab; INF, infliximab; GOL, golimumab; ADA, adalimumab; ETA, etanercept; PBO, placebo
Green indicates where comparisons are considered to be significant.

Table 58: SUCRA Rankings for BASDAI (Fixed Effects): Biologic Experienced

Rank	Treatment	SUCRA
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dose

BASFI Results: Biologic-Naïve

No NMA of BASFI outcomes tofacitinib and secukinumab could be conducted in biologic-naïve patients as BASFI was not reported in the MEASURE studies.

BASFI Results: Biologic Experienced

Network for BASFI in Biologic Experienced

Two studies were included in the network for BASFI (COAST-W and A3921120). Changes from baseline in BASFI by study and treatment arm are shown in Table 59.

Table 59: Change from Baseline in BASFI Among Study Arms: Biologic Experienced

Study Name	Intervention	N	Change from Baseline (SE)
A3921120	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
COAST-W	Ixekizumab	114	-1.7 (0.20)
	Placebo	104	-0.6 (0.20)

Key: SE: standard error

Model Fit and Heterogeneity

Due to the sparsity of studies, only the fixed effects model was fit ([redacted]). Tests for heterogeneity were not performed since no more than one study contributed to each direct comparison in the network.

Results for BASFI

[redacted]

Table 60: Fixed Model for BASFI without Baseline Risk Adjustment: Biologic Experienced

	Fixed Effects	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: CrI, credible interval; Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment.

ASDAS Results: Biologic-Naïve

No NMA of ASDAS outcomes tofacitinib and secukinumab could be conducted in biologic-naïve patients as ASDAS was not reported in the MEASURE studies.

ASDAS Results: Biologic Experienced

Network for ASDAS in Biologic Experienced

Two studies were included in the network for BASFI (COAST-W and A3921120). Changes from baseline in BASFI by study and treatment arm are shown in Table 59.

Table 61: Change from Baseline in ASDAS Among Study Arms: Biologic Experienced

Study Name	Intervention	N	Change from Baseline (SE)
A3921120	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
COAST-W	Ixekizumab	114	-1.1 (0.10)
	Placebo	104	-0.1 (0.10)

Key: SE: standard error

Model Fit and Heterogeneity

Due to the sparsity of studies, only the fixed effects model was fit ([redacted]). Tests for heterogeneity were not performed since no more than one study contributed to each direct comparison in the network.

Results for ASDAS: Biologic Experienced

Results for changes in baseline are shown in Table 62.

[redacted]

Table 62: Fixed Model for ASDAS without Baseline Risk Adjustment: Biologic Experienced

	Fixed Effects	
	Tx vs PBO Diff (95% CrI)[a]	**Tof vs Tx Diff (95% CrI)[b]**
Ixekizumab	**-1.0 (-1.3, -0.7)**	0.2 (-0.3, 0.6)
Tofacitinib	**-0.8 (-1.2, -0.5)**	--

Key: CrI, credible interval; Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment.

ASQoL Results: Biologic-naive

A total of 5 studies were included in the network (Table 63).

Figure 20: Network for Tofacitinib and Secukinumab

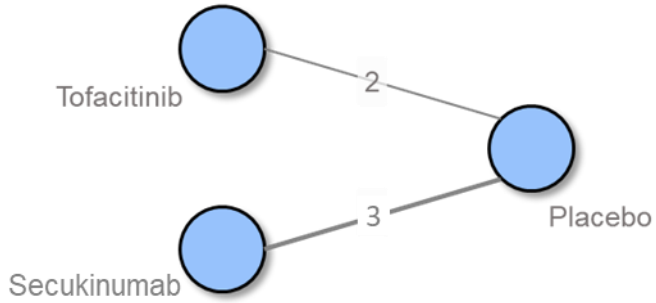


Table 63: Change from Baseline in ASQoL Among Study Arms

Study Name	Intervention	N	Change from Baseline (SE)
A3921119	Tofacitinib	[redacted]	[redacted]
A3921119	Placebo	[redacted]	[redacted]
A3921120	Tofacitinib	[redacted]	[redacted]
A3921120	Placebo	[redacted]	[redacted]
MEASURE 2	Secukinumab	[redacted]	[redacted]
MEASURE 2	Placebo	[redacted]	[redacted]
MEASURE 4	Secukinumab (L)	[redacted]	[redacted]
MEASURE 4	Secukinumab (NL)	[redacted]	[redacted]
MEASURE 4	Placebo	[redacted]	[redacted]
MEASURE 5	Secukinumab	[redacted]	[redacted]
MEASURE 5	Placebo	[redacted]	[redacted]

Key: SE, standard error

Model Fit and Heterogeneity

Fixed effects and random effects models were fit and model fit statistics are shown in Table . Random effects models did not result in an improved fit compared to fixed effects models with and without baseline risk adjustment. Therefore, the fixed effects models without and with baseline risk adjustment are therefore presented here. Low-to-moderate heterogeneity was observed between MEASURE 2, MEASURE 3 and MEASURE 4 studies for the secukinumab loading dose comparator (Table 64).

Table 64. Model Fit Statistics for ASQoL Fixed and Random Effects Models Without Baseline Risk Adjustment

	Without Baseline Risk Adjustment		With Baseline Risk Adjustment	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Between-study variance (τ^2)	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: DIC, deviance information criterion

Table 65: Heterogeneity Statistics for ASQoL Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2, MEASURE 4, MEASURE 5	[redacted]	[redacted]
Tofacitinib vs Placebo	A3921119, A3921120	[redacted]	[redacted]

Key: L, loading dose

Results for ASQoL

[redacted]

Table *66*: Fixed Effects and Random Effects Models for ASQoL

	Fixed Effects Without Baseline Risk Adjustment		Fixed Effects With Baseline Risk Adjustment	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: CrI, credible interval; Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.
Green indicates where treatment is superior to the alternative treatment.

Table 67. League Table for ASQoL: Fixed Effects without Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--

SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PCB, placebo
Green indicates where comparisons are considered to be significant.

Table 68. League Table for ASQoL: Fixed Effects with Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PCB, placebo
Green indicates where comparisons are considered to be significant.

Table 0-69. SUCRA Rankings for ASQoL: Fixed Effects Without and With Baseline Risk Adjustment

Without Baseline Risk Adjustment			With Baseline Risk Adjustment		
Rank	**Treatment**	**SUCRA**	**Rank**	**Treatment**	**SUCRA**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

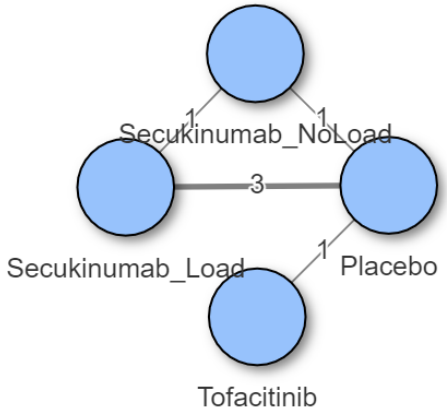
Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dose

ASQoL Results: Biologic Experienced

Network for ASQoL in Biologic Experienced

Four studies were included in the network for ASQoL (MEASURE 2, MEASURE 4, MEASURE 5 and A3921120) (Figure 21). Changes from baseline in ASQoL by study and treatment arm are shown in Table 70.

Figure 21: Network Diagram for ASQoL: Biologic Experienced



Key: NoLoad, no loading dose; Load, loading dose

Table 70: Change from Baseline in ASDAS Among Study Arms: Biologic Experienced

Study Name	Intervention	N	Change from Baseline (SE)
A3921120	Tofacitinib	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]
MEASURE 2	Secukinumab (L)	28	-2.4 (0.80)
	Placebo	29	-0.5 (0.80)
MEASURE 4	Secukinumab (L)	31	-2.7 (0.80)
	Secukinumab (NL)	32	-3.5 (0.79)
	Placebo	34	-2.5 (0.76)
MEASURE 5	Secukinumab (L)	28	-2.4 (0.80)
	Placebo	31	-2.3 (0.80)

Key: SE, standard error; L, loading dose; NL, no loading dose

Model Fit and Heterogeneity

Due to the sparsity of studies, only the fixed effects model was fit ([redacted]). Moderate heterogeneity was observed between the MEASURE 2, MEASURE 4, and MEASURE 5 studies with respect to comparisons of secukinumab (loading dose) with placebo (Q = 3.17, p = 0.2050, I^2 = 36.9%) (Table 69).

Table 71: Heterogeneity Statistics for ASDAS Comparisons: Biologic Experienced

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2, MEASURE 4, MEASURE 5	[redacted]	[redacted]

Results for ASQoL: Biologic Experienced Population

Results for changes in baseline are shown in Table 72.

[redacted]

Table 72: Fixed Model for ASDAS Without Baseline Risk Adjustment: Biologic Experienced

	Fixed Effects	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: FE, fixed effects; RE, random effects; DIC, deviance information criterion; Tx, treatment; Tof, tofacitinib Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.

SF-36 PCS Results: Biologic-naive

Network for SF-36 PCS

A total of 5 studies were included in the network. Changes in SF-36 PCS from baseline input data are in
Table .

Figure 22: Network for Tofacitinib and Secukinumab

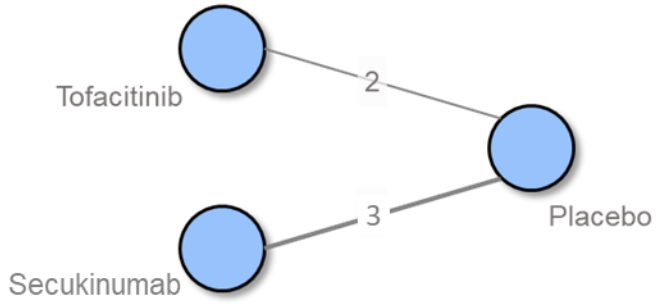


Table 73: Change from Baseline in SF-36 PCS Among Study Arms

Study Name	Intervention	N	Change from Baseline (SE)
A3921119	Tofacitinib	[redacted]	[redacted]
A3921119	Placebo	[redacted]	[redacted]
A3921120	Tofacitinib	[redacted]	[redacted]
A3921120	Placebo	[redacted]	[redacted]
MEASURE 2	Secukinumab (L)	44	7.5 (1.00)
MEASURE 2	Placebo	45	3.0 (1.00)
MEASURE 4	Secukinumab (L)	6.74	6.7 (0.80)
MEASURE 4	Secukinumab (NL)	85	7.7 (0.81)
MEASURE 4	Placebo	83	5.2 (0.82)
MEASURE 5	Secukinumab (L)	240	7.4 (0.43)
MEASURE 5	Placebo	122	4.9 (0.60)

Key: SE, standard error; NL, no loading dose; L, loading dose

Model Fit and Heterogeneity

Fixed effects and random effects models were fit and model fit statistics are shown in Table 74, with and without baseline risk adjustment. The fixed effect model with baseline risk adjustment was preferred due to a lower DIC. Only the fixed-effects model with baseline risk adjustment is presented; random effects models were not conducted on this outcome due to poor convergence. Moderate heterogeneity was observed for secukinumab (loading dose) vs. placebo (Table 75).

Table 74. Model Fit Statistics for SF-36 Fixed and Random Effects Models Without and With Baseline Risk Adjustment

	Without Baseline Risk Adjustment		With Baseline Risk Adjustment	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects
Between-study variance (τ^2)	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: DIC, deviance information criterion

Table 75: Heterogeneity Statistics for SF-36 PCS Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2, MEASURE 4, MEASURE 5	[redacted]	[redacted]

Tofacitinib vs Placebo	A3921119, A3921120	[redacted]	[redacted]

Key: L, loading dose

Results for SF-36 PCS

Results for the fixed effects model with baseline risk adjustment is shown in Table 76. All comparisons vs. placebo show higher SF-36 PCS increases from baseline for active treatments.

Table 76: Fixed Effects and Random Effects Models for SF-36 PCS

	Fixed Effects with Baseline Risk Adjustment	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: Tx, treatment; Tof, tofacitinib; Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment
b. Values greater than 0 favor alternative treatment
Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment.

Table 77. League Table for SF-36 PCS: Fixed Effects with Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PCB, placebo
Green indicates where comparisons are considered to be significant.

Table 0-78. SUCRA Rankings for SF-36 PCS: Fixed Effects with Baseline Risk Adjustment

With Baseline Risk Adjustment		
Rank	**Treatment**	**SUCRA**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

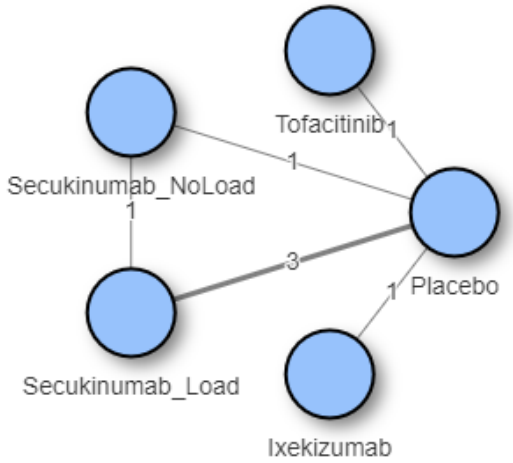
Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dose

SF-36 PCS Results: Biologic Experienced

Network for SF-36 PCS: Biologic Experienced

Five studies were included in the network for SF-36 PCS (COAST-W, MEASURE 2, MEASURE 4, MEASURE 5 and A3921120) (Figure 23). Changes from baseline in SF-36 PCS by study and treatment arm are shown in Table 79.

Figure 23. Network Diagram for SF-36 PCS Change from Baseline: Biologic Experienced



Key: NoLoad, no loading dose; Load, loading dose

Table 79: Proportion of Patients SF-36 PCS Among Study Arms: Biologic Experienced

Study Name	Intervention	N	Change from Baseline (SE)
A3921120	Placebo	[redacted]	[redacted]
	Tofacitinib	[redacted]	[redacted]
COAST-W	Placebo	104	1.4 (0.80)
	Ixekizumab	114	6.6 (0.80)
MEASURE 2	Placebo	29	0.3 (1.20)
	Secukinumab (L)	24	4.5 (1.20)
MEASURE 4	Placebo	28	4.0 (1.21)
	Secukinumab (L)	31	5.2 (1.28)
	Secukinumab (NL)	32	6.5 (1.26)
MEASURE 5	Placebo	31	3.3 (1.11)
	Secukinumab (L)	65	7.3 (0.86)

Key: NL, no loading dose; L, with loading dose; SE, standard error

Model Fit and Heterogeneity

Due to the few studies in the network and low heterogeneity (Table 80), a fixed effects model without baseline risk adjustment was fit for the comparison.

Table 80: Heterogeneity Statistics for SF-36 Change from Baseline Comparisons: Biologic Experienced

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]

Key: L, with loading dose

Results for SF-36 PCS: Biologic Experienced

Results from the fixed effects model are shown in Table 79.

[redacted]

Table 81: Fixed Model for Change from Baseline Without Baseline Risk Adjustment for SF-36 PCS: Biologic Experienced

	Fixed Effects	
	Tx vs PBO Diff (95% CrI)[a]	Tof vs Tx Diff (95% CrI)[b]
Ixekizumab	[redacted]	[redacted]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]

Key: CrI, credible interval; Tx, treatment; Tof, tofacitinib Diff, difference from baseline; PBO, placebo; NL, no loading dose; L, loading dose
a. Values less than 0 favor the treatment.
b. Values greater than 0 favor alternative treatment.

Adverse Event-Related Discontinuation Results: Biologic-naive

Network for AE-Related Discontinuation

A total of 5 studies were included in the network. Notably, no studies provided subgroup analyses in accordance with bDMARD/TNFi exposure for AE-related

discontinuation. Therefore, results also include studies of mixed population (i.e., A3921120, MEASURE 2, MEASURE 4, and MEASURE 5) (Table 82).

Figure 24: Network for Tofacitinib and Secukinumab

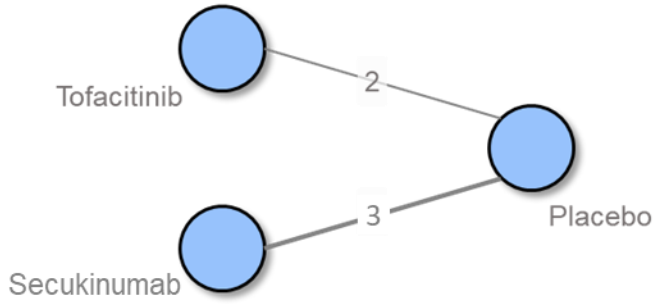


Table 82. Proportion of Patients with AE-Related Discontinuation Among Study Arms

Study Name	Intervention	N	R (%)
A3921119	Tofacitinib	[redacted]	[redacted]
A3921119	Placebo	[redacted]	[redacted]
A3921120[a]	Tofacitinib	[redacted]	[redacted]
A3921120[a]	Placebo	[redacted]	[redacted]
MEASURE 2[a]	Secukinumab (L)	72	5 (6.9)
MEASURE 2[a]	Placebo	74	4 (5.4)
MEASURE 4[a]	Secukinumab (L)	116	1 (0.9)
MEASURE 4[a]	Secukinumab (NL)	117	2 (1.7)
MEASURE 4[a]	Placebo	117	1 (0.9)
MEASURE 5[a]	Secukinumab (L)	304	2 (0.7)
MEASURE 5[a]	Placebo	153	1 (0.7)

Key: N, total denominator; R, total numerator; L, loading dose; NL, no loading dose
a. Data from mixed population.

Model Fit and Heterogeneity

Model fit statistics for both the fixed effects models with and without baseline risk adjustment are shown in Table 83. Random effects models were not fitted due to poor convergence. The fixed effects model with baseline risk adjustment was preferred due to a lower DIC.

Table 83. Model Fit Statistics for AE-Related Discontinuation Fixed Effects Models

	Fixed Effects	
	Without Baseline Risk Adjustment	With Baseline Risk Adjustment

DIC	[redacted]	[redacted]

Key: DIC, deviance information criterion

The I^2 for comparisons vs placebo were high for a number of comparisons, indicating evidence for some heterogeneity between MEASURE 2, MEASURE 4, and MEASURE 5 (Table 84).

Table 84: Heterogeneity Statistics for AE-Related Discontinuation Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]
Tofacitinib vs Placebo	A3921119(30), A3921120(17)	[redacted]	[redacted]

Key: L, loading dose

Results for AE-Related Discontinuation

Results for the fixed effect models with and without baseline risk adjustment are provided in Table 83.

[redacted]

Table 85: Fixed Effects Models Without and With Baseline Risk Adjustment for AE-Related Discontinuation

	FE without Baseline Risk Adjustment		FE with Baseline Risk Adjustment	
	Tx vs PBO OR (95% CrI)[a]	Tof vs Tx OR (95% CrI)[b]	Tx vs PBO OR (95% CrI)[a]	Tof vs Tx OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: Tx, treatment; Tof, tofacitinib; OR, odds ratio; PBO, placebo; NL, no loading dose; L, loading dose
a. ORs greater than 1 favor the treatment.
b. ORs greater than 1 favor tofacitinib
c. Green indicates where treatment is superior to the alternative treatment. Pink indicates where tofacitinib is inferior to the alternative treatment

All pairwise comparisons are depicted in Table .

[redacted]

Table 86. League Table for AE-Related Discontinuation: Fixed Effects with Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	SEC (L)	--	--
SEC (NL)	[redacted]	[redacted]	SEC (NL)	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PCB, placebo

Table 87. SUCRA Rankings for AE-Related Discontinuation

Fixed Effects with Baseline Risk Adjustment		
Rank	**Treatment**	**SUCRA**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dos

Results for Serious Adverse Events: Biologic-naive

Network for Serious Adverse Events

A total of 5 studies were included in the network. No studies provided subgroup analyses in accordance with bDMARD/TNFi exposure for serious adverse events. Therefore, results also include studies of mixed population (ie, A3921120, MEASURE 2, MEASURE 4, and MEASURE 5) (Table 86).

Figure 25: Network for Tofacitinib and Secukinumab

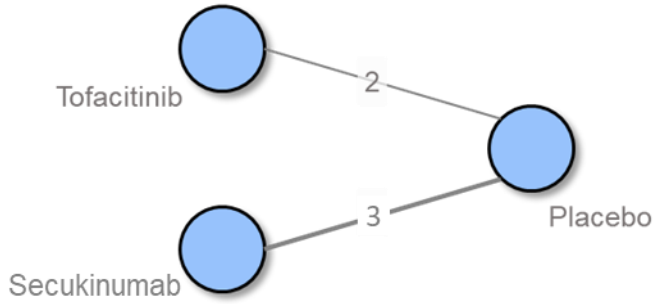


Table 88. Proportion of Patients with AE-Related Discontinuation Among Study Arms

Study Name	Intervention	N	R (%)
A3921119	Tofacitinib	[redacted]	[redacted]
A3921119	Placebo	[redacted]	[redacted]
A3921120[a]	Tofacitinib	[redacted]	[redacted]
A3921120[a]	Placebo	[redacted]	[redacted]
MEASURE 2[a]	Secukinumab (L)	72	4 (5.6)
MEASURE 2[a]	Placebo	74	5 (6.8)
MEASURE 4[a]	Secukinumab (L)	116	2 (1.7)
MEASURE 4[a]	Secukinumab (NL)	117	2 (1.7)
MEASURE 4[a]	Placebo	117	4 (3.4)
MEASURE 5[a]	Secukinumab (L)	304	10 (3.3)
MEASURE 5[a]	Placebo	153	3 (2)

Key: N, total denominator; R, total numerator; L, loading dose; NL, no loading dose
a. Data from mixed population

Model Fit and Heterogeneity

A fixed effects model without baseline risk adjustment was conducted ([redacted]). Baseline risk adjustment was not conducted due to zero values in the placebo arm for A3921120. Random effects models were not fit due to poor convergence. Low-to-moderate heterogeneity was observed for tofacitinib vs. placebo comparisons (Table 87).

Table 89: Heterogeneity Statistics for Serious AE Comparisons

Comparison	Studies	Q-statistic (p-value)	I^2
Secukinumab (L) vs Placebo	MEASURE 2(37, 38), MEASURE 4(39), MEASURE 5(40)	[redacted]	[redacted]

Tofacitinib vs Placebo	A3921119(30), A3921120(17)	[redacted]	[redacted]

Key: L, loading dose

Results for Serious Adverse Events

Results for the fixed effect model is provided in Table 88.

[redacted]

Table 90: Fixed Effects Model for Serious AEs

	Tx vs PBO OR (95% CrI)[a]	Tof vs Tx OR (95% CrI)[b]
Secukinumab (NL)	[redacted]	[redacted]
Secukinumab (L)	[redacted]	[redacted]
Tofacitinib	[redacted]	**

Key: CrI, credible interval; Tx, treatment; Tof, tofacitinib; OR, odds ratio; PBO, placebo; NL, no loading dose; L, loading dose
a. ORs greater than 1 favor the treatment.
b. ORs greater than 1 favor tofacitinib.

Table 91. League Table for Serious AEs: Fixed Effects Without Baseline Risk Adjustment

	TOF			
SEC (L)	[redacted]	**SEC (L)**	--	--
SEC (NL)	[redacted]	[redacted]	**SEC (NL)**	--
PCB	[redacted]	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; SEC (L), secukinumab with loading dose; SEC (NL), secukinumab without loading dose; PCB, placebo

Table 92. SUCRA Rankings for Serious AEs

Fixed Effects with Baseline Risk Adjustment		
Rank	**Treatment**	**SUCRA**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Key: SUCRA, surface under the cumulative ranking curve; NL, no loading dose; L, loading dos

A14. Heterogeneity in pairwise comparisons was assessed and presented as Cochran's Q and I^2 (Appendix D page 26).

a) Please provide details of the software used to calculate these, including all data and code so that analyses can be reproduced.

Please find all heterogeneity results are provided in Appendix 4 Tofa-vs-ADA-heterogeneity.xlsx.

b) ***Please comment on the reliability of the estimates obtained for Q and I^2, given the small number of studies available for each comparison (von Hippel 2015;(43) West et al 2010(44))***

All heterogeneity results are provided in Appendix 4 Tofa-vs-ADA-heterogeneity.xlsx. Heterogeneity assessments which are inherently associated with low power to detect statistically significant heterogeneity. However, I2 above 50% were found among the adalimumab trials for several outcomes. No investigation of the sources of heterogeneity was performed since all adalimumab trials have been evaluated and included in prior HTA assessments, and thus assumed to be sufficiently similar for comparison.

A15. Given that there are only a few studies per comparison (maximum of 4 in any network, with some networks having fewer), there is not enough information to reliably estimate the between-study heterogeneity (a minimum of 5 studies per comparison is recommended for adequate estimation – see Gelman, 2006(45)). This results in very wide 95% CrI for the between-study heterogeneity in most networks.

a) ***Please comment on the plausibility of the values included in the 95% CrI for the between-study heterogeneity for the binary outcomes presented in Appendix D, with reference to Table 5.2 in Spiegelhalter et al 2004.(46)***

The detailed results of the NMAs are provided in Appendix 3, under file names AS NMA results for ERG.xlsx. While the CrIs for differences in outcomes are wider in the RE networks, the point estimates produced by the FE and RE models are very similar across all outcomes. Pfizer considers the results of both the RE and FE models informative and suitable for decision making.

b) ***If there is a prior reason to believe that the included studies are likely to be heterogeneous but there is not enough information to reliably estimate the heterogeneity, the use of informative prior distributions for the between-study heterogeneity may be justified (Dias et al 2018,(47) sections 2.3.2 and 6.3.2). Please present results using an appropriate empirically informed or minimally informative prior distribution for the***

random effects models for each outcome considered in the NMAs (Dias et al 2018,(47) sections 2.3.2 and 6.3.2; Röver et al 2021(48))

Although the heterogeneity test found some evidence of heterogeneity for some outcomes, all ADA studies have been included in evidence synthesis conducted for previous HTAs suggesting that the studies were considered sufficiently similar for pooling.

A16. Page 86 of the main company submission provides justification for selecting the random effects NMA models stating that *"The DIC was comparable between the various models and under those circumstances, the RE model was selected, as it has previously been recommended for interpreting outcomes of NMAs with fewer than 10 studies."*

a) **Please provide a reference for the recommendation to use RE models in NMAs with fewer than 10 studies as it is known that between-study heterogeneity is poorly estimated in RE models where there are less than 5 studies per comparison (Gelman, 2006(45)), thus interpretation is limited and uncertainty can be over-estimated (Dias et al 2018,(47) sections 2.3.2 and 6.3.2).**

b) **Please also provide a reference recommending that the most complex model (in this case RE) be chosen when DIC are comparable, as common practice when DIC differences are small (less than 3 to 5 points) is to choose the simplest model as it is easier to interpret and the DIC suggests no evidence justifying the additional complexity (TSD2(49) an Dias et al 2018,(47) section 3.3).**

As explained in section 3.9.2 page 86 of the company submission, Bayesian models for both FE and RE models were conducted for all networks and these are presented in Appendix D 1.2 page 45. Heterogeneity was observed for many outcomes (defined as an I2 value above 50%) and the DIC and total residual deviance were calculated for all FE and RE networks where possible and these are presented in

Appendix D. Pfizer considers the results of both the RE and FE models informative and suitable for decision making.

A17. PRIORITY QUESTION: For all outcomes, please present the NMA results for each comparator intervention vs. tofacitinib in the form of a forest plot including the relative effect estimates and CrIs for all the different NMA models considered presented as different lines (see for example, Fig 4 in Oba et al. 2018(50)).

Forest plot results are presented in Appendix 3 in files named 'Binary AS NMA results for ERG.xlsx' and 'Binary AS NMA results for ERG.xlsx'.

A18. PRIORITY QUESTION: The company fit a placebo-adjusted model to adjust for differences in the mean placebo effect across studies. For all outcomes for which an adjusted model was fitted, please also provide plots of odds ratios (for all comparators) against the odds of a response in the placebo arm (on the log-scale – see TSD3,(51) Figure 7) so that the appropriateness of the adjustments can be assessed. Please also comment on which studies are contributing information to the estimation of the adjustment slope and how this should be interpreted.

Please see the plots of odds ratios below. In terms of contribution to the estimation of the adjustment slope, all studies contribute to the slope since all ADA and TOF studies are placebo-controlled.

Figure 26 Log-odds ratio plots (please note this figure contains AIC information)

Indirect and mixed treatment comparisons – data

A19. On page 25 of the Appendices document (Appendix D) it is stated that "For safety data, studies with zero-cell counts were excluded if no other study provided patient counts for at least one of the arms." Please clarify the

meaning of this sentence and exactly when studies were excluded, giving examples if appropriate.

This was pre-specified method for the network meta-analysis, which did not apply to the analyses in the end.

A20. Appendix D, section D.1.2 (page 25) states that NMAs were carried out including studies according to bDMARD/TNFi exposure. However, it is unclear exactly which data from which studies are included in each of these analyses, which provide the results labelled "mixed" and "naïve" in the Appendices (e.g. tables 19-22 in Appendix D and similar tables for other outcomes).

a) ***For each of the "mixed" and "naïve" NMAs for which results are presented, please provide details of the exact data included.***

A summary of the data inputs for the NMA are presented in Table .

b) ***Given the points in questions A5, A10 and A13 on positioning of tofacitinib, please also consider presenting data and NMA results for the biologic-experienced population.***

NMA results for the biologic-experienced population are included in response to question A13. Only outcomes for IL-17is could be presented as no data for biologic-experienced patients could be identified from trials of TNFis. Upadacitinib and filgotinib were not part of the final scope and therefore not included in the decision problem of this appraisal and therefore, they were not included in the analyses of the submission, as discussed in response to question A10.

Table 93: Data Inputs for the NMA

NMA	Outcome	Trial	Data Inputs		
			Intervention	N	R (%)
Biologic-naïve	ASAS20	ATLAS	Adalimumab	208	111 (53.4)
			Placebo	107	20 (18.7)
		COAST-V	Adalimumab	90	53 (58.8)
			Placebo	87	35 (40.2)
		Huang 2014	Adalimumab	229	154 (67.2)
			Placebo	115	35 (30.4)
		M03-606	Adalimumab	38	18 (47.4)
			Placebo	44	12 (27.3)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib		
			Placebo		
	ASAS40	ATLAS	Adalimumab	208	83 (39.9)
			Placebo	107	14 (13.1)
		COAST-V	Adalimumab	90	32 (35.6)
			Placebo	87	16 (18.4)
		Huang 2014	Adalimumab	229	102 (44.5)
			Placebo	115	11 (9.6)
		M03-606	Adalimumab	38	17 (44.7)
			Placebo	44	4 (9.1)
		A3921119	[redacted]	[redacted]	[redacted]
		A3921120			
	BASDAI50	COAST-V	Adalimumab	90	29 (32)
			Placebo	87	15 (17.0)
		Huang 2014	Adalimumab	229	114 (49.8)
			Placebo	115	19 (16.5)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib		
			Placebo		

NMA	Outcome	Trial	Data Inputs		
			Intervention	N	R (%)
	Δ BASDAI	ATLAS	Adalimumab	34	-2.6 (0.20)
			Placebo	35	-0.8 (0.20)
		COAST-V	Adalimumab	25	-2.5 (0.21)
			Placebo	25	-1.4 (0.22)
		Huang 2014	Adalimumab	44	-2.8 (0.13)
			Placebo	45	-1.4 (0.18)
		Hu 2012	Adalimumab	229	-3.6 (0.42)
			Placebo	115	-2.0 (0.45)
		M03-606	Adalimumab	52	-2.0 (0.35)
			Placebo	51	-0.6 (0.30)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib		
			Placebo		
	Δ BASFI	ATLAS	Adalimumab	208	-1.9 (0.15)
			Placebo	107	-0.4 (0.22)
		COAST-V	Adalimumab	90	-2.1 (0.21)
			Placebo	87	-1.2 (0.22)
		Hu 2012	Adalimumab	26	-1.9 (0.41)[a]
			Placebo	20	-1.0 (0.45)[a]
		M03-606	Adalimumab	38	-1.3 (0.34)[a]
			Placebo	44	-0.3 (0.30)[a]
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib		
			Placebo		
	Δ BASMI	ATLAS	Adalimumab	208	-0.5 (0.10)
			Placebo	107	0.1 (0.10)
		Huang 2014	Adalimumab	229	-0.5 (0.04)
			Placebo	115	-0.2 (0.07)
		M03-606	Adalimumab	38	-0.3 (0.14)a
			Placebo	44	0.1 (0.11)a
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		

NMA	Outcome	Trial	Data Inputs		
			Intervention	N	R (%)
		A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	Δ ASQoL	ATLAS	Adalimumab	208	-3.2 (0.30)
			Placebo	107	-1.0 (0.40)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	Δ SF-36v2 PCS	ATLAS	Adalimumab	208	6.9 (0.60)
			Placebo	107	1.6 (0.80)
		Huang 2014	Adalimumab	229	6.6 (0.42)
			Placebo	115	4.0 (0.59)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	Δ SF-36v2 MCS	ATLAS	Adalimumab	208	2.7 (0.70)
			Placebo	107	2.4 (1.00)
		Huang 2014	Adalimumab	229	2.8 (0.88)
			Placebo	115	5.1 (0.65)
		A3921119	Tofacitinib	[redacted]	[redacted]
			Placebo		
		A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
Mixed[b]	**ASAS20**	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	ASAS40	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	BASDAI50	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	Δ BASDAI	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		
	Δ BASFI	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo		

NMA	Outcome	Trial	Data Inputs		
			Intervention	N	R (%)
	Δ BASMI	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo	[redacted]	[redacted]
	Δ ASQoL	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo	[redacted]	[redacted]
	Δ SF-36v2 PCS	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo	[redacted]	[redacted]
	Δ SF-36v2 MCS	A3921120	Tofacitinib	[redacted]	[redacted]
			Placebo	[redacted]	[redacted]

a. Standard errors were estimated by imputing standard deviations from other arms where standard deviation was provided. A weighted average of standard deviations was calculated for active and placebo arms separately. Where standard errors or standard deviations were not provided in the study, the weighted average of the placebo or active comparator arm was used.

b. As the above data inputs for biologic-naïve patients were included in the mixed NMA, only mixed patients from A3921120 are included here (to replace biologic-naïve patients from A3921120).

A21. Please clarify whether Hu 2012 was included or excluded from the NMAs of BASDAI and BASFI change from baseline. For BASDAI, page 40 in Appendix D states 7 trials were included in the NMA, whereas the footnote to Table 13 states this study was excluded (meaning only 6 studies in the NMA). For BASFI, page 41 in Appendix D states 6 trials were included in the NMA, whereas the footnote to Table 14 states this study was excluded (meaning only 5 studies in the NMA). If the study was excluded, please present results of sensitivity analyses where it is included (and vice versa if included).

The Hu et al. study was excluded from the analyses. This was excluded due to unclear biases and reasons to suspect the possibility of important bias (see aectionB.3.9 in company submission). Sensitivity analysis including the BADSAI and BASFI data reported in unadjusted analyses are presented in Appendix 3 under file name 'Continuous AS NMA results for ERG.xlsx'

When the Hu et al. study had been excluded in sensitivity analyses for TA383 (excluded due to risk of bias), it was found that outcomes between the sensitivity analyses and main analysis (whereby the study had been included) were similar (see Table 94).

Table 94: Results for Adalimumab vs. Placebo (TA383 NMA): Continuous Outcomes at 10-16 Weeks

Intervention	Analysis	BASDAI Score		BASFI Score	
		# Trials (# pts)	Mean difference in change from baseline (95%CrI)	# Trials (# pts)	Mean difference in change from baseline (95%CrI)
Adalimumab	Main	3 (705)	-1.55 (-1.88 to -1.22)	2 (390)	-1.25 (-1.63 to -0.87)
	Sensitivity (exc. Hu et al. 2012)	2 (659)	-1.55 (-1.89 to -1.21)	1 (344)	-1.28 (-1.68 to -0.88)

Source: (52)

A22. PRIORITY QUESTION: The main company submission document (page 98) states that 3 NMAs were considered for adverse events/safety outcomes: overall discontinuation, AE related discontinuation and SAE.

a) AE related discontinuation: In Appendix F it is stated that an NMA could not be conducted due to all placebo arms having zero cells. Please

attempt to carry out this NMA by adding a continuity correction to the studies with one zero cell (excluding the study where both arms had a zero) – see Dias et al 2018,(47) section 6.3. Alternatively, a frequentist NMA can also be conducted for this outcome using Stata ('network') or R (e.g., 'netmeta').

Results of the frequentist analysis have been carried out using R (netmeta). The results below indicate that the likelihood of AE related discontinuation with tofacitinib is [redacted]. However, [redacted] AE related discontinuations [redacted].

Table 95: Discontinuations due to AEs Among Studies Identified for the NMA

	Placebo arm		Adalimumab/ tofacitinib arm	
	Placebo (n=)	Event rate, n (%)	Intervention (n=)	Event rate, n(%)
COAST-V	Placebo (n=86)	0 (0.0)	Adalimumab (n=90)	1 (1.1)
M03-606	Placebo (=44)	0 (0.0)	Adalimumab (n=38)	0 (0.0)
Huang 2014	Placebo (n=115)	0 (0.0)	Adalimumab (n=229)	4 (1.7)
van der Heijde 2017	Placebo (n=51)	3 (5.9)	Tofacitinib (n=52)	1 (1.9)
A3921120	Placebo (n=136)	1 (0.7)	Tofacitinib (n=133)	3 (2.3)

Figure 27: Forest plot results of AE related discontinuation (please note this figure contains AIC information)

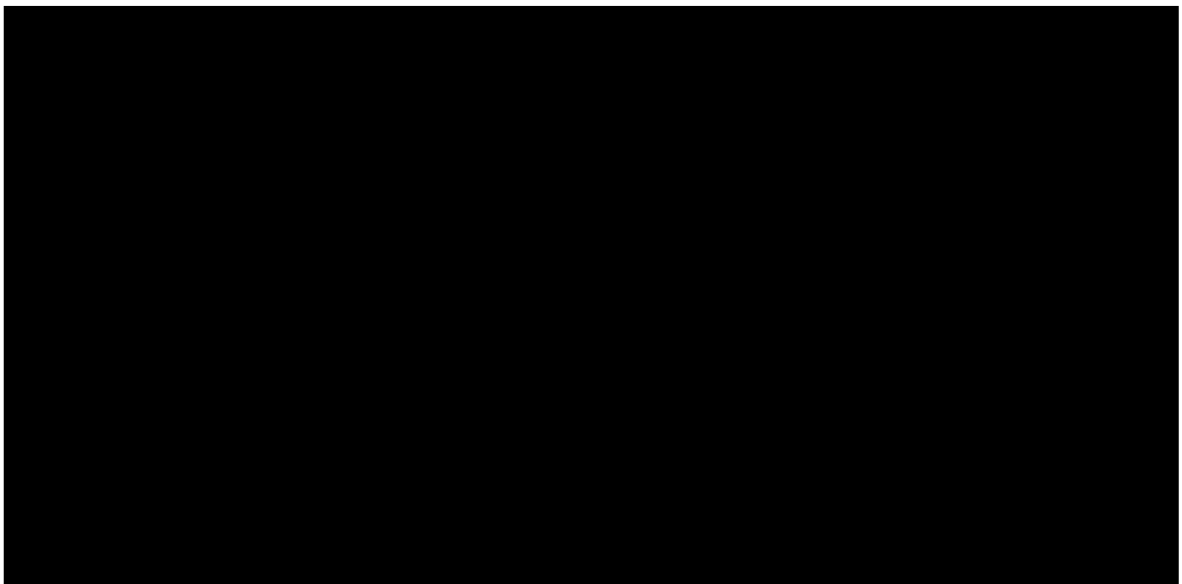


Table 96. League Table for AE-Related Discontinuation: Fixed Effects with Baseline Risk Adjustment

	TOF		
ADA	[redacted]	ADA	
PCB	[redacted]	[redacted]	PCB

Key: TOF, tofacitinib; ADA, adalimumab; PCB, placebo

b) SAE: In Appendix F it is stated that an NMA was conducted with data presented in Table 56 (appendix F). However, no results are actually presented and the main company submission states that "No NMA was conducted as there were significant issues with autocorrelation when adjusting for baseline risk." Please present results for all unadjusted NMAs and explain what attempts were made to try to resolve the autocorrelation issues in the adjusted models (for example was the covariate appropriately centred?)

The proportions of patients experiencing serious AEs according to study among the 4 identified studies reporting this safety outcome are shown in Table 93. Due to the sparse data and few studies available, only a fixed effects model was fit ([redacted]). The model used 30,000 iterations after thinning by every 40th iteration and a burn-in of 10,000 iterations. Compared to placebo, an [redacted] observed for tofacitinib and adalimumab. Compared to adalimumab, tofacitinib had a [redacted] of serious AEs; however this was not significant. Notably, a [redacted], results should be interpreted with caution. Unadjusted results are presented in Appendix 3 under file name 'Safety AS NMA results for ERG.xlsm'. No attempt was made to resolve the autocorrelation issues with the adjusted models.

Table 97: Serious AEs by Study and Treatment Arm

Study	TX.1	N.1	N.1 (%)	TX.2	N.2	N.2 (%)
Huang 2014	Placebo	115	1 (0.9)	Adalimumab	229	1 (0.4)
COAST-V	Placebo	86	0 (0)	Adalimumab	90	3 (3.3)

A3921119	Placebo	51	2 (3.9)	Tofacitinib	52	1 (1.9)
A3921120	Placebo	136	0 (0)	Tofacitinib	133	2 (1.5)

c) Overall discontinuation: no data are presented for this NMA, but results are available. Please provide details of all data used for this outcome (this may already be included in response to question A11).

Five studies were included in the NMA for discontinuation. Discontinuation according to study and treatment are provided in Table 94. Heterogeneity statistics are provided in Table 95.

Table 98: Discontinuation by Study and Treatment Arm

Study	TX.1	N.1	N.1 (%)	TX.2	N.2	N.2 (%)
Huang 2014	Placebo	115	4 (3.5)	Adalimumab	229	8 (3.5)
COAST-V	Placebo	86	0 (0)	Adalimumab	90	2 (2.2)
ATLAS	Placebo	107	5 (4.7)	Adalimumab	208	6 (2.9)
A3921119	Placebo	51	4 (7.8)	Tofacitinib	52	1 (1.9)
A3921120	Placebo	136	4 (2.9)	Tofacitinib	133	5 (3.8)

Moderate heterogeneity was observed for tofacitinib vs. placebo, with higher rates of discontinuation for placebo observed in A3921119 compared to A3921120 (7.8% vs. 2.9%) and higher rates of discontinuation for tofacitinib arms for A3921120 compared to A3921119 (3.8% and 1.9%).

Table 99: Heterogeneity Assessment by Comparison (Cochrane's Q and I2)

Comparison		
	Q (p-value)	I2
Tofacitinib vs. Placebo	[redacted]	[redacted]
Adalimumab vs. Placebo	[redacted]	[redacted]

The fixed effects model without baseline risk adjustment was fit with 10,000 burn-in iterations and 30,000 subsequent iterations after thinning by every 10th iteration. With baseline risk adjustment, a 60,000 burn-in was used, followed by 100,000 iterations and thinning by every 50th iteration. The random effects model without baseline risk adjustment was fit after a 30,000-iteration burn-in, followed by 90,000 sampled iterations after thinning by every 50th iteration. The random effects model with

baseline risk adjustment was fit after a 60,000-iteration burn-in, followed by 70,000 sampled iterations after thinning by every 100th iteration.

Model fit statistics are provided in Table 96. The fixed effects model with baseline risk adjustment provided the best fit and is therefore preferred.

Table 100: Model Fit Statistics

Analysis	Without Baseline Risk Adjustment			With Baseline Risk Adjustment		
	FE	RE		FE	RE	
	DIC	DIC	τ2 (95% CrI)	DIC	DIC	τ2 (95% CrI)
Mixed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Not reported due to poor convergence

Pairwise comparisons are shown in Table 97 across all models. The preferred fixed effects model with baseline risk adjustment suggested similar odds of discontinuation vs. placebo for tofacitinib and adalimumab. Pairwise comparisons between both treatments did not suggest significant differences.

Table 101: Pairwise Comparisons

	Mixed, OR (95% CrI)			
	FE, Unadj.	FE, BL-Adj.	RE, Unadj.	RE, BL-Adj.
Tofacitinib vs Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab vs Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs. Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]

*Not reported due to poor convergence

d) Please consider a class effect for IL-17s (see also question A10) and repeat the safety NMAs requested in points a)-c) using a class model for IL-17s, if appropriate (a correction for zero cells may not be needed if a class model is used).

Results for biologic naïve patients versus secukinumab are provided in response to question A13.

Section B: Clarification on cost-effectiveness data

Adverse events costs

B1. PRIORITY QUESTION: Please consider the expected implications of the monitoring, prevention (e.g., statins, use of compression devices, etc.) and of the management and treatment of: i) relevant short-term adverse events identified in the clinical trial (justify inclusions and exclusions in the updated cost-comparison requested in question B2), and ii) long-term adverse events identified in questions A3 and A4.

It is expected that the monitoring requirements would be similar across all bDMARDs, therefore, costs of monitoring was not taken into account in the economic analysis. However, under question B2c we present a scenario analyses where extra-costs were included for annual cost of lipid profile monitoring for tofacitinib.

The monitoring requirement for tofacitinib is expected to be similar as for other biologics, regardless of the safety warnings. Regular blood monitoring is required for biologics as part of routine care every 3 months (27). A lipid test between 4-8 weeks is also recommended for tofacitinib. As expected, the inclusion of annual lipid parameter monitoring has a very limited impact on the final results.

As included in question A3, there is no evidence to suggest that tofacitinib used in line with the current label (including restrictions for those with certain risk factors) would result in a discrepancy in AEs relative to TNFi-treated patients. Real word data research from the CorEvitas registry in the US (post-authorisation safety study) compared 5-year safety data of tofacitinib versus biologics in the RA population (non-CV risk-enriched population), showing similar incidence rates for MACE, serious infections, malignancy, venous thromboembolism and death between both cohorts. The NMA also did not show statistically significant difference between tofacitinib and adalimumab in terms of safety outcomes, as presented in response to question A22b and between tofacitinib and secukinumab as presented in response to question A13, therefore the costs of adverse events was not taken into account in the economic analysis.

B2. PRIORITY QUESTION: For relevant short-term adverse events identified in the clinical trial and for each of the long-term adverse events identified in question A3 consider the following:

a) ***Comment on the likelihood of the occurrence of these events, with and without treatment with tofacitinib, in both the overall population (as per the marketing authorisation) and in the population restricted by the MHRA.***

The population of the marketing authorisation is for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. We would like to reiterate that the marketing authorisation is not limited to patients with no risk factors present and Pfizer believes that the clinical and cost effectiveness of tofacitinib in AS is unlikely to be significantly different between the at-risk and other patients.

Please refer to the points on the MHRA safety update under question A3.

b) ***In the cost-comparison model, please include the costs of any additional baseline risk assessments that may be implemented in clinical practice (such as cardiovascular risk assessment, i.e., QRISK3) prior to initiating treatment with tofacitinib. For cardiovascular risk, this should at least include lipid profiling, blood pressure measurement, body weight measurement, and diabetes tests.***

As explained in response to question A3-5, Pfizer does not anticipate the MHRA safety update to have an impact on the clinical or cost effectiveness of tofacitinib. Regular monitoring of CV risk factors is recommended for all patients with spondyloarthritis (including AS), therefore it would affect both arms of the cost-comparison equally (27).

c) ***In the cost-comparison model, please include the likelihood and costs of additional routine monitoring for patients on treatment that may be implemented in clinical practice, such as annual lipid profile monitoring.***

Please refer to answer to questions B1 for details regarding monitoring of adverse events. Please find in Table a scenario of the updated base case analysis, including

annual cost of lipid profile monitoring for tofacitinib (for details regarding the updated base case please refer to answer to question B3). As expected, the inclusion of annual lipid parameters monitoring has a very limited impact on the final results compared to **the updated base case presented in Table .**

Table 102: Scenario including annual lipid profile monitoring

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Initiation year					
Acquisition cost	£9,001 [redacted]	£8,265	£10,234	£ 17,422	£15,519
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£674	£669	£669	£669	£669
Total cost	9,675 [redacted]	£8,934	£10,904	£18,091	£16,188
Difference versus tofacitinib (list price)	-	£741	-£1,229	-£8,416	-£6,513
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent years (per year)					
Acquisition cost	£9,001 [redacted]	£8,265	£7,949	£15,899	£14,675
Administration cost	£-	£-	£-	£	£-
Monitoring cost	£331	£328	£328	£ 328	£328
Total cost	£9,332 [redacted]	£8,593	£8,277	£16,227	£15,003
Difference versus tofacitinib (list price)	-	£739	£1,054	-£6,895	-£5,671
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

d) ***In the cost-comparison model, please include the likelihood and costs of further preventative actions, such as treatment with statins for patients experiencing elevated lipid levels.***

As explained in response to question A3-5 and B1 there is no data to support that the costs of monitoring and adverse events would be different amongst the biologics in AS.

e) ***In the cost-comparison model, please include the likelihood of occurrence of adverse events and the costs of their diagnosis, of their management and treatment (e.g., low molecular weight heparin, warfarin for venous thromboembolic disease).***

As explained in response to question A3-5 and B1 there is no data to support that the costs of monitoring and adverse events would be different amongst the biologics in AS.

Drug administration costs

B3. Clinical advisors to the ERG indicate that most patients will have received training in the use of self-injecting subcutaneous biologics at previous lines of treatment and are unlikely to require re-training. Moreover, some companies provide self-injection training free of cost. Can the company provide evidence of whether such training is being provided in the NHS at either first or subsequent lines of treatment?

Administration costs for s.c. injections were included in previous appraisals, such as TA383 and the secukinumab NICE appraisal (TA407). There it was assumed, both by the company and the ERG, that a one-off administration cost for s.c. therapies would equal to £43.00 (in case of first administration only, following 1 hour of nurse training on first administration, PSSRU 2015). Because of these precedents, this has been the assumption in our original base case as explained in section B.4.2.4.

However, in response to this clarification question we present updated analyses (Table), where training cost for self-injecting treatments are not included. In addition, in the updated base case outcomes, several of the following clarification questions have been addressed, as outlined/ summarised in Table 103.

Table 103 Updates included in the current (updated) base case

Treatment	Previous base case	Updated base case	Question addressed
Administration cost for self-injecting treatments (cost of training)	£42	£0	B3
TB test	£9.47	£62.52	B5
Unit cost for antinuclear antibody testing and dsDNA antibody tests	£2.53	£7.40	B6
IL-17 inhibitors	Not included in the analysis	Included in the analysis	B10
Assumption for duration of 1 year	365 or 365.25 days	365.25 days	C2
Updated National Schedule of NHS Cost values	As per national schedule NHS costs FY19/20 v15	As per national schedule NHS costs FY19/20 (no version specified)	**C3**

Table 104: Updated Base Case Results

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Initiation year					
Acquisition cost	£9,001 [redacted]	£8,265	£10,234	£17,422	£15,519
Administration cost	£0	£0	£0	£-	£0
Monitoring cost	£672	£669	£669	£669	£669
Total cost	£9,673 [redacted]	£8,934	£10,904	£18,091	£16,188
Difference versus tofacitinib (list price)	-	£739	-£1,231	-£8,418	-£6,515
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent years (per year)					
Acquisition cost	£9,001 [redacted]	£8,265	£7,949	£15,899	£14,675
Administration cost	£0	£0	£0	£0	£0

Monitoring cost	£328	£328	£328	£328	£328
Total cost	£9,329 [redacted]	£8,593	£8,277	£16,227	£15,003
Difference versus tofacitinib (list price)	-	£736	£1,052	-£6,897	-£5,674
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

B4. Clinical advisors to the ERG indicate that adherence to daily oral treatment is likely to be an important issue in clinical practice for tofacitinib, particularly in relation to alternative treatments which are delivered by monthly injection. Please comment on how this could affect treatment effectiveness and patient outcomes, for example if doses are missed.

In Study A3921120 compliance with dosing administration was verified by accounting of returned containers and investigational product at each visit. The results shown that there was no incidence of overcompliance in either the tofacitinib or placebo group throughout the treatment period.

[redacted].

Table 105 Study A3921120 Summary of Treatment Compliance - Safety Analysis Set (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)

Collected Visit	Treatment	N	Mean	SD	SE	Min	Q1	Median	Q3	Max
Week 2	Tofacitinib 5 mg BID	[redacted]								
	Placebo									
Week 4	Tofacitinib 5 mg BID									
	Placebo									
Week 8	Tofacitinib 5 mg BID									
	Placebo									
Week 12	Tofacitinib 5 mg BID									
	Placebo									
Week 16	Tofacitinib 5 mg BID									

	Placebo	[redacted]								
Week 24	**Tofacitinib 5 mg BID**	[redacted]								
	Placebo -> Tofacitinib 5 mg BID	[redacted]								
Week 32	**Tofacitinib 5 mg BID**	[redacted]								
	Placebo -> Tofacitinib 5 mg BID	[redacted]								
Week 40	**Tofacitinib 5 mg BID**	[redacted]								
	Placebo -> Tofacitinib 5 mg BID	[redacted]								
Week 48	**Tofacitinib 5 mg BID**	[redacted]								
	Placebo -> Tofacitinib 5 mg BID	[redacted]								

N: Number of subjects with observation at each time point.
Visit of Week 2 was Dosing Period of Baseline to Week 2, visit of Week 4 was Dosing Period of Week 2 to Week 4, etc.
Safety Analysis Set (SAFETY) – All subjects who were randomized and received at least one dose of the investigational product.
The study treatment compliance (%) was derived from the total number of doses actually taken divided by the total number of doses expected to take per dosing period as recorded in Oral Dosing Case Report Form page.
Source: Study A3921120 Clinical Study report Table 14.4.1.7

Table 106 Study A3921120 Incidence of Study Drug Non-Compliance by Visit Up to Week 16 - Safety Analysis Set (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)

		Tofacitinib 5 mg BID (N=133)						**Placebo (N=136)**						**Total (N=269)**					
		Incidence			**Cumulative Incidence**			**Incidence**			**Cumulative Incidence**			**Incidence**			**Cumulative Incidence**		
Number (%) of Subjects	**Collected Visit**	**N1**	**n1**	**%**	**N2**	**n2**	**%**	**N1**	**n1**	**%**	**N2**	**n2**	**%**	**N1**	**n1**	**%**	**N2**	**n2**	**%**
Under-compliance [a]	Week 2	[redacted]																	
	Week 4																		
	Week 8																		
	Week 12																		
	Week 16																		
Over-compliance [b]	Week 2																		
	Week 4																		
	Week 8																		
	Week 12																		
	Week 16																		
Met Under-compliance criterion [c]																			

N1=number of subjects with observation at each visit and was the denominator for incidence calculation. n1=number of subjects who met the criteria within the visit.
N2=number of subjects with observation from baseline through the visit of interest and was the denominator for cumulative incidence calculation. n2=number of subjects who met the criteria at least once from baseline through the visit of interest.
[a] Less than 80% compliance with tablet.
[b] Over-compliance (>120%) with investigational product (intentional or accidental). [c] Less than 80% compliance with tablet on 2 consecutive visits.
Visit of Week 2 was Dosing Period of Baseline to Week 2, visit of Week 4 was Dosing Period of Week 2 to Week 4, etc.
Source: Study A3921120 Clinical Study report Table 14.4.1.8

Table 107 **Study A3921120 Incidence of Study Drug Non-Compliance by Visit Up to Week 48 - Safety Analysis Set (Week 16 Analysis) (Data Cutoff 19Dec2019, Data Snapshot 29Jan2020)**

		Tofacitinib 5 mg BID (N=133)						Placebo -> Tofacitinib 5 mg BID (N=136)						Total (N=269					
		Incidence			Cumulative Incidence			Incidence			Cumulative Incidence			Incidence			Cumulative Incidence		
Number (%) of Subjects	Collected Visit	N1	n1	%	N2	n2	%	N1	n1	%	N2	n2	%	N1	n1	%	N2	n2	%
Under-compliance [a]	Week 2	[redacted]																	
	Week 4																		
	Week 8																		
	Week 12																		
	Week 16																		
	Week 24																		
	Week 32																		
	Week 40																		
	Week 48																		
Over-compliance [b]	Week 2																		
	Week 4																		
	Week 8																		
	Week 12																		
	Week 16																		
	Week 24																		
	Week 32																		
	Week 40																		
	Week 48																		
Met Under-compliance criterion																			

N1=number of subjects with observation at each visit and was the denominator for incidence calculation. n1=number of subjects who met the criteria within the visit.
N2=number of subjects with observation from baseline through the visit of interest and was the denominator for cumulative incidence calculation. n2=number of subjects who met the criteria at least once from baseline through the visit of interest.
[a] Less than 80% compliance with tablet.
[b] Over-compliance (>120%) with investigational product (intentional or accidental). [c] Less than 80% compliance with tablet on 2 consecutive visits.
Visit of Week 2 was Dosing Period of Baseline to Week 2, visit of Week 4 was Dosing Period of Week 2 to Week 4, etc.
Safety Analysis Set (SAFETY) – All subjects who were randomized and received at least one dose of the investigational product.
Source: Study A3921120 Clinical Study report Table 14.4.1.9

As described in section B.4.2.2 of the main submission, the NMA did not show a statistically significant difference in discontinuation rates between tofacitinib and adalimumab in the mixed population.

In real world data, an international collaboration of registries (JAK-pot registry), 6,063 patients initiated a JAKi, 13,879 initiated TNFi, 2,348 initiated abatacept, and 3,231 initiated an IL-6i. When compared to TNFi-treated patients, JAKi-treated patients tended to have a higher adjusted overall drug retention (53).

As mentioned in the answer for question A5b, studies have shown that patients with other rheumatological conditions prefer oral therapies over injectables due to ease of administration (10).

Monitoring costs

B5. Clinical advice to the ERG suggests that the Tuberculosis Heaf test is no longer commonly used to detect latent TB, with the interferon gamma release assay (IGRA) typically used in patients prior to use of immunosuppressive treatments. Please update the monitoring costs to reflect current clinical practice regarding TB testing.

The monitoring cost for tuberculosis testing was updated as requested using the unit cost for QuantiFERON – TB Gold-In Tube (QFT-GIT) reported in the interferon gamma release assay (IGRA) HTA report and inflated to year 2021 cost using the NHS cost inflation index (NHSCII) as specified in Table (55, 56).

Table 108: IGRA test costs

TB testing in previous and current model	Heaf test	QFT-GIT
Tuberculosis test	£9.47	Original value £58 (2019) inflated to 2021 £62.52

IGRA: Interfefon Gamma Release Assay; QFT-GIT: QuantiFERON—TB Gold In-Tube test; TB: Tuberculosis

B6. Please justify the use of the DAPS05 (Haematology)(57) currency code for the unit cost antinuclear antibody testing and dsDNA tests. These tests are immunological assays and would be more appropriately costed as DAPS06 – please amend in the model or provide an alternative justification for keeping the current costs.

As recommended by the ERG, the unit costs for antinuclear antibody test and dsDNA antibody tests were updated using the DAPS 06 (immunology) code in the updated base case presented in Table .

Time horizon

B7. PRIORITY QUESTION: Please state and justify the time horizon used in the cost-comparison model. Please update the model to allow considering

alternative time horizons (with costs disaggregated by year). Include sensitivity analyses for a time horizon equal to mean treatment duration, and for time horizons of 2, 5 and 10 years.

The model was updated, as suggested by the ERG, allowing to test for time horizons between 1 and 10 years. Table to Table include the results of the sensitivity analyses, using a 2-, 5- and 10-years' time horizon. Note that the disaggregated cost per initial and subsequent years (per year) will not differ between the different time horizons scenarios.

Table 109: 2 Year Time Horizon

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Initial year					
Acquisition cost	£9,001 [redacted]	£8,265	£10,234	£17,422	£15,519
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£672	£669	£669	£669	£669
Total cost	£9,673 [redacted]	£8,934	£10,904	£18,091	£16,188
Difference versus tofacitinib (list price)	-	£739	-£1,231	-£8,418	-£6,515
Difference versus tofacitinib (discounted price)	-	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent years (year 2, cost per year)					
Acquisition cost	£9,001 [redacted]	£8,265	£7,949	£15,899	£14,675
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£328	£328	£328	£328	£328
Total cost	£9,329 [redacted]	£8,593	£8,277	£16,227	£15,003
Difference versus tofacitinib (list price)	-	£736	£1,052	-£6,897	-£5,674
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Overall results over time horizon (2 years)					
Acquisition cost	£18,002 [redacted]	£16,530	£18,184	£33,321	£30,194
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£1,000	£998	£998	£998	£998
Total cost	£19,002 [redacted]	£17,528	£19,181	£34,318	£31,192
Difference versus tofacitinib (list price)	-	£1,475	-£179	-£15,316	-£12,189
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

Table 110: 5 Year Time Horizon

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Initial year					
Acquisition cost	£9,001 [redacted]	£8,265	£10,234	£17,422	£15,519
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£672	£669	£669	£669	£669
Total cost	£9,673 [redacted]	£8,934	£10,904	£18,091	£16,188
Difference versus tofacitinib (list price)	-	£739	-£1,231	-£8,418	-£6,515
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent years (year 2 to 5, cost per year)					
Acquisition cost	£9,001 [redacted]	£8,265	£7,949	£15,899	£14,675
Administration cost	£0	£0	£0	£0	£0

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Monitoring cost	£328	£328	£328	£328	£328
Total cost	£9,329 [redacted]	£8,593	£8,277	£16,227	£15,003
Difference versus tofacitinib (list price)	-	£736	£1,052	-£6,897	-£5,674
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Overall results over time horizon (5 years)					
Acquisition cost	£45,006 [redacted]	£41,325	£42,032	£81,016	£74,220
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£1,985	£1,982	£1,982	£1,982	£1,982
Total cost	£46,991 [redacted]	£43,307	£44,014	£82,998	£76,202
Difference versus tofacitinib (list price)	-	£3,683	£2,977	-£36,008	-£29,211
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

Table 111: 10 Year Time Horizon

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
Initial year					
Acquisition cost	£9,001 [redacted]	£8,265	£10,234	£17,422	£15,519
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£672	£669	£669	£669	£669
Total cost	£9,673 [redacted]	£8,934	£10,904	£18,091	£16,188
Difference versus tofacitinib (list price)	-	£739	-£1,231	-£8,418	-£6,515

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg	Ixekizumab
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent years (year 2 to 10, cost per year)					
Acquisition cost	£9,001 [redacted]	£8,265	£7,949	£15,899	£14,675
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£328	£328	£328	£328	£328
Total cost	£9,329 [redacted]	£8,593	£8,277	£16,227	£15,003
Difference versus tofacitinib (list price)	-	£736	£1,052	-£6,897	-£5,674
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Overall results over time horizon (10 years)					
Acquisition cost	£90,012 [redacted]	£82,651	£81,778	£160,509	£147,596
Administration cost	£0	£0	£0	£0	£0
Monitoring cost	£3,625	£3,623	£3,623	£3,623	£3,623
Total cost	£93,637 [redacted]	£86,274	£85,401	£164,132	£151,219
Difference versus tofacitinib (list price)	-	£7,364	£8,237	-£70,494	-£57,581
[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]

Discontinuation rates

B8. PRIORITY QUESTION: Please update the cost-comparison model to allow differential discontinuation rates for each intervention, and include an analysis

using the updated discontinuation rate for tofacitinib provided in response to question A5 d).

Please refer to the response to question A5 d). Discontinuation rates were similar between adalimumab and tofacitinib over follow-up (please refer to question A22 c) and between tofacitinib and IL-17s (please refer to question A13).

Other costs and analyses

B9. Symptoms of extra-articular manifestations in AS may impact on treatment decisions including selection of biologic drugs and whether to continue treatment. Please comment on the appropriateness of excluding uveitis outcomes and their associated costs from the cost-comparison model.

No notable differences in extra-articular manifestations were observed for tofacitinib and placebo in A3921119 and A3921120. Further, neither study had been sufficiently powered to detect a significant difference between arms. In TA383, the committee had been aware that potential differences between TNFis in their effects on extra-articular manifestations and that this may have cost implications, but it was noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis.

Please also refer to response to question A8 on data on extra-articular manifestations.

B10. PRIORITY QUESTION: Please provide a cost-comparison analysis of tofacitinib with IL-17 inhibitors for i) biologic-naïve and ii) biologic experienced populations, including the electronic version of the model used to perform it. Please also provide results for the additional sensitivity analyses requested in questions B2 and B5 to B9, as well as for any other additional cost-comparison analysis the company decides to present in response to the points for clarification.

The results of the cost comparison versus IL-17 inhibitors have been included throughout section B, contextually addressing the relevant clarification questions.

Our estimations for the treatment costs for secukinumab includes two possible dosing regimens: one using 150mg per dose, and one using an increased dose of 300mg in the maintenance phase, in line with the marketing authorisation.

In terms of a comparison between biologic-naïve and biologic experience populations, the costs of treatment, monitoring and administration are expected to be the same across these populations.

Section C: Textual clarification and additional points

Confidential marking

C1. Why is "cost comparison" marked as CIC in table 2, page 16 of the main company submission (3 instances) when in the submission title and elsewhere it is clearly stated that a cost-comparison analysis is presented?

This was a typographical error and the CIC marking can be lifted on cost-comparison throughout the document.

Textual clarifications

Cost-comparison

C2. Please apply a consistent value for the duration of one year in the modelled drug cost calculations. The ERG's preference would be to apply 365.25 days consistently across all calculations.

Please see the results updated to apply 365.25 throughout section B and in the attached updated excel file.

C3. The ERG was unable to validate a number of unit cost estimates for the monitoring costs in Table 31 of the main company submission against the National Schedule of NHS Costs 2019-2020 main schedule.(57) The discrepancies identified are illustrated in Table , where the column identified as 'ERG' records the value identified by the ERG in the original source, available in the NHS website. Please correct the unit costs as appropriate.

The values included in the initial model were derived from the National Schedule of NHS costs 2019-2020 v 15 (latest available at the time of submission) and included in

the submission reference pack. The current updated model includes unit cost updated to the National Schedule of NHS cost aligned with the version reviewed by the ERG group, for consistency (57, 58).

Missing References

C4. PRIORITY QUESTION: Please provide a copy of the company clinical expert interview (Ref # 6), which was referenced in the main company submission.

Please see the summary of the clinical expert interview provided in the reference pack, under the title: Pfizer Clinical Expert Interview Summary [ACIC]

Tables

Table 112 Unit costs for monitoring (adapted from table 31, main company submission)

Item	Unit cost		Source in the Company Submission
	CS	ERG	
Full blood count	£2.58	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).
Erythrocyte sedimentation rate	£2.58	£2.53	
Liver function test	£1.22	£1.20	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS04 – clinical biochemistry).
Urea and electrolytes	£1.22	£1.20	
Chest X-Ray	£32.53	£32.72	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Direct access plain film (Currency code DAPF).
Tuberculosis test	£9.47	NA	Rodgers et al. (2011) cost (£8.01) inflated to 2019/20 prices based on the HCHS/NHSCII pay and prices inflation index in PSSRU Unit Costs of Health and Social Care 2020.
Antinuclear antibody	£2.58	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).
Double-stranded DNA test	£2.58	£2.53	
Specialist visit	£155.06	£149.14*	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Consultant-led non-admitted face-to-face attendance, follow-up. (Currency code WF01A).

Item	Unit cost		Source in the Company Submission
	CS	ERG	
Lipid parameters	**£2.58**	**£2.53**	**National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology). (58)**

***Unit cost for Rheumatology visit; Abbreviations: CS: company main submission; DNA: deoxyribonucleic acid; HCHS: hospital & community health services; NA, not applicable; NHS: National Health Service; NHSCII: NHS cost inflation index; PSSRU: Personal Social Services Research Unit.**

Table 113 ERG concerns about the company systematic review bibliographic database searches (Question A2)

Issue	Details
Weaknesses in searching for the intervention	**Lack of Subject Headings / Missing Subject Headings for Intervention:** o There are no MeSH terms or Emtree terms for any the Intervention terms represented in S2. o The lack of subject headings used despite many relevant subject headings available could have missed relevant material. For instance, the following are Emtree headings which could have been used: etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, secukinumab, ustekinumab, ixekizumab, netakimab, apremilast, bimekizumab, upadacitinib, filgotinib, etoricoxib, and tofacitinib. Moreover, the following are MeSH headings which could have been used: Etanercept, Infliximab, Adalimumab, Certolizumab Pegol, Ustekinumab, Etoricoxib **Missing Free-Text Terms for Drug Trade Names:** o Missing Infliximab trade name: Avsola. o Missing Upadacitinib trade name: Rinvoq. **Missing Free-Text Terms for Biosimilars:** Adalimumab: Solymbic, Hulio, Hadlima, Kromeya, Imraldi, Hefiya, Amgevita, Idacio, Halimatoz, Amsparity, Trudexa, Yuflyma, ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293 Etanercept: Nepexto, Etacept, Etanar, TuNEX, Yisaipu, Lifmior, BX2922, CHS-0214, ENIA11, GP2013, GP2015, HD203, LBEC0101, PRX-106, SB4 Infliximab: Flixabi, Zessly, **Missing Field Codes for Interventions:** Both Medline and Embase via ProQuest have a field code for Substance (SUBST) and a field code for Trade Name (TN) but these have not been utilised as field codes for the free-text terms for interventions on line S2.
Weaknesses in searching for the condition	**Missing Free-Text Terms for Condition:** o The limited coverage of terms used for the condition risks missing relevant material. The following synonyms for the condition were not used: ankylosing spondylarthritides, ankylosing spondylarthritis, ankylosing spondyloarthritides, ankylosing spondyloarthritis, bechterew disease, bechterew's disease, bechterews disease, marie struempell disease, marie-struempell disease, rheumatoid spondylitis, ankylating spondylitis, ankylopoietic spondylarthritis, ankylopoietic spondylitis, ankylosing

	spine, ankylosing spondilitis, ankylosing spondylarthritis, ankylosing spondylarthrosis, ankylosis spondylitis, ankylotic spondylitis, bekhterev disease, morbus bechterew, spinal ankylosis, spine ankylosis, spondylarthritis ankylopoietica, spondylarthritis ankylosans, spondylarthrosis ankylopoietica, spondylitis ankylopoetica, spondylitis ankylopoietica, spondyloarthritis ankylopoietica, vertebral ankylosis, Rheumatoid arthritis of spine, bekhterev's disease, and spondylosis deformans. **Missing Emtree Heading for Condition:** o On Embase via ProQuest, the subject heading spondylarthritis has not been used, despite its relevance. **Unclear Search Design for Free-Text Search Term for Condition:** o Also, please can (TI,AB("axial spondyloarthritis") AND TI,AB(radiographic)) from S1 (Appendix D, p. 12) be explained – why isn't the condition searched for in its own right? And why 'radiographic' in particular rather than a truncated term?

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Tofacitinib for treating ankylosing spondylitis ID3865

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	National Axial Spondyloarthritis Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	NASS is the only charity in the UK solely dedicated to supporting people living with axial spondyloarthritis (axial SpA) including ankylosing spondylitis. We provide information and support to people with the condition, as well as campaigning for better treatment and care. NASS is funded by a variety of voluntary sources including membership, individual fundraisers, charitable trusts, legacies and industry funding. We receive no statutory or government funding. NASS currently has 4,072 members, the majority of which have axial SpA (AS).
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes Aspiring to Excellence Quality Improvement programme 30,000.00 All Party Parliamentary Group secretariat 16,000.00 Act on Axial SpA: A Gold Standard Time to Diagnosis 287,681.00 Aspiring to Excellence Quality Improvement programme 30,000.00 All Party Parliamentary Group secretariat 16,000.00 Round table policy meeting in axial SpA 11,900.00 Aspiring to Excellence Quality Improvement programme 30,000.00 Aspiring to Excellence Quality Improvement programme 30,000.00

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We carried out a survey of members and followers to seek views on the comparator upadacitinib. Unfortunately due to time constraints and current commitments in research we were not able to conduct a further survey relating to tofacitinib. The responses received for upadacitinib are relevant to tofacitinib.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Axial Spondyloarthritis (axial SpA) refers to inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis *may or may not* be present. Within axial SpA there are two groups: **Ankylosing Spondylitis (AS):** Where the x-ray changes are clearly present. **Non-radiographic axial spondyloarthritis (nr-axSpA):** Where x-ray changes are *not* present but you have symptoms.

	Axial SpA is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. People with ankylosing spondylitis often develop spinal fusion which is irreversible. We asked people to tell us about how having axial spondyloarthritis had impacted on their life. 92% said that it had impacted very (49%) or somewhat negatively (43%) . Most commonly people cited the pain and fatigue which impacted on their ability to carry on with everyday life. Many have had to stop working. The resulting effect on mental health was also a strong factor. *"I am in pain, every day. I suffer with severe fatigue and "brain fog" regularly. I can no longer work full time and am considering medical retirement at 45."* *"My whole lifestyle has been impacted by AS it has turned me from a healthy, active & happy person into the complete opposite I'm now disabled, inactive & suffer with poor mental health."* *"I was completely disabled by the pain. I lost my home and my career as a sports journalist and have never got that back. I spent 15 years barely able to function, on and off. I'd be dead without Humira; I was rationally considering suicide before being prescribed anti-TNF in 2004. I was on Etanercept but it didn't really work. I finally switched to Humira in 2015 and am generally much better, but still have a lot of nerve pain."* *"My income has been less and therefore my pension is now less. It had affected my family relationships too."* *"Divorce, premature retirement due to ill health, financial implications, no children, difficulty with relationships/ social life, difficulty exercising and travelling. lack of energy to do daily tasks of living."* *"It's affected me massively as I used to be a professional dancer and I compare myself to then and now and it can be quite mentally tough to deal with - it becomes a before life and a now with AS life."*

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	We asked respondents to tell us which medications they were taking and to let us know their satisfaction levels. The majority were taking biologics (67%) and / or anti inflammatories (52%), with 14% needing opioids such as tramadol or morphine. Simple pain relief such as paracetamol (16%) and co-codamol (22%) were also being used. Respondents were relatively satisfied with their current medications, although just 15% were completely satisfied overall and 14% were completely satisfied with how it works for them. 26% of people were either were completely unsatisfied (6%) or somewhat unsatisfied (20%) with their medications overall. The weighted averages, when scored out of five were: • Overall satisfaction 3.44 • How well it works 3.49 • Side effects 3.54 • Convenience 3.71 Given the huge negative impact axial SpA is having on lives, there is clear room for improvement in medications.
8. Is there an unmet need for patients with this condition?	Yes. Whilst the corner stones of treatment are anti inflammatory medication and exercise, there are those who cannot tolerate non-steroidal anti inflammatories (NSAIDs) and 20% of people do not respond to the biologic drugs currently available (TNF and IL17-a inhibitors). A new drug targeting a different enzyme could mean an alternative treatment to enable people with ankylosing spondylitis to be able to exercise more easily and to live a fuller life.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When asked what advantages the technology may have over current medications: • 84% liked that is in tablet form • 54% thought it would be easy to store • 43% liked that it had already been used in other conditions • 30% thought the advantage came from the new formulation • 29% thought it sounded like it works well. A link to the information on the NICE website was included but no specific information on efficacy was included. In the open ended responses, respondents thought it may be cheaper than other biologics which are injected and that it would help those who have needle phobia. It was also mentioned that it would be easier to carry when travelling as current injected medications need to be stored in a refrigerator or cool bag.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We also asked what concerns people might have and what they thought the disadvantages might be: • 75% of people were concerned about the side effects • 58% of people worried it wouldn't be as effective as current medications • 21% thought there may be issues with it being a new formula In the open ended responses, there were concerns about eligibility, the dosage, if a return to other treatment would be permitted if this was not effective, the possible interactions with other medications and if it caused infections.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are a number of people who might benefit more such as those who: • Cannot tolerate NSAIDs • Have not responded to other biologics • Have a needle phobia • Live in shared accommodation and do not have access to their own fridge to store other biologic drugs • Travel lots for work or want to go travelling.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. Those from lower income households who may need to share access to communal areas. This would also apply to students and young people who often have shared accommodation.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • JAK inhibitors have been well received by people with axial SpA as an alternative biologic drug • There are advantages to the drug, in particular its tablet form • Along with upadacitinib it is a good alternative to other biologic treatments • There are some worries around the side effect / safety • There were also convcerns about being offered another biologic drug if this was not effective

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Tofacitinib for treating ankylosing spondylitis ID3865

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Spondyloarthritis Special Interest Group (SIG)**
2. Name of organisation	**British Society for Rheumatology (BSR)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology (BSR)**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce disease activity Improve pain and functioning Improve quality of life (QoL) Reduce fatigue Reduce structural progression and radiographic change
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Reduction in BASDAI and spinal pain VAS by 2 points

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in those patients who fail to respond to TNF inhibitors and / or IL-17 inhibitors. There is also a need for oral small molecule inhibitors for AS
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In general or specialist outpatient clinics
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance on management of spondyloarthritis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Pathway of care is generally well-defined but there may be local variability depending on local expertise, resources and agreement re funding of targeted therapies

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Provide additional option for medical management in those patients who have not responded to standard therapies
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes as an additional therapeutic option, managed in the same setting as current care
• How does healthcare resource use differ between the technology and current care?	This is a first oral small molecule agent in the treatment of ankylosing spondylitis.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – especially for patients who have not responded to currently approved medical therapies
• Do you expect the technology to increase length of life more than current care?	no
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, for patients who have not responded to currently approved medical therapies
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	May be easier for some patients, being orally administered rather than s/c
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Disease activity measures to decide if patient is eligible to start and continue treatment, used in same way as for existing therapies. No additional testing.
15. Do you consider that the use of the technology will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – improve pain, disease activity and quality of life for patients who have not responded to used therapies currently in use
• Is the technology a 'step-change' in the management of the condition?	Yes – drug with new mechanism of action
• Does the use of the technology address any particular unmet need of the patient population?	There is significant unmet need for a group of patients who fail to respond, or lose response, to TNF or IL-17 inhibitors and this technology will offer an alternative treatment option.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As with all the medical therapies used in AS, the risk of side effects will be weighed against the impact of uncontrolled disease. For some patients, active disease impairs their quality of life significantly and justifies the use of a new medication with potential side effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes ASAS responses, also CRP, quality of life measures, fatigue and metrology.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No new safety risks identified that we are aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA383, TA407, TA497, TA718 and TA719?	Phase 3 trial published 2021
21. How do data on real-world experience compare with the trial data?	Not aware of real world data

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • Significant unmet need exists for patients with AS, due to failure of response or loss of response to existing therapies and this technology offers an additional therapeutic option • First of its kind oral small molecule targeted therapy for AS • Provides convenience for patients as simple administration compared to injections • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 20 May 2022.**

Completing this form

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Rheumatology**
3. Job title or position	**Consultant Physician & Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it

encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce disease activity Improve pain and functioning Improve quality of life (QoL) Reduce fatigue Reduce structural progression and radiographic change

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in BASDAI and spinal pain VAS by 2 points
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in those patients who fail to respond to TNF inhibitors and / or IL-17 inhibitors. There is also a need for oral medication for AS
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	In general or specialist rheumatology outpatient clinics
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance on management of spondyloarthritis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Pathway of care is generally well-defined but there may be local variability depending on local expertise, resources and agreement re funding of targeted therapies

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Provide additional option for medical management in those patients who have not responded to standard therapies
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes as an additional therapeutic option, managed in the same setting as current care
• How does healthcare resource use differ between the technology and current care?	This is a first oral small molecule agent in the treatment of ankylosing spondylitis
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary Care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	N/A
13. Do you expect the technology to provide clinically meaningful	Yes – especially for patients who have not responded to currently approved medical therapies

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	NO
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, for patients who have not responded to currently approved medical therapies
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	NO
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	May be easier for some patients, being orally administered rather than s/c

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Disease activity measures to decide if patient is eligible to start and continue treatment, used in same way as for existing therapies. No additional testing.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – improve pain, disease activity and quality of life for patients who have not responded to used therapies currently in use

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – drug with new mechanism of action
• Does the use of the technology address any particular unmet need of the patient population?	There is significant unmet need for a group of patients who fail to respond, or lose response, to TNF or IL-17 inhibitors and this technology will offer an alternative treatment option.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As with all the medical therapies used in AS, the risk of side effects will be weighed against the impact of uncontrolled disease. For some patients, active disease impairs their quality of life significantly and justifies the use of a new medication with potential side effects.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes ASAS responses, also CRP, quality of life measures, fatigue and metrology.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No new safety risks identified that I am aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal	Phase 3 trial published 2021

guidance TA383, TA407, TA497, TA718 and TA719?	
23. How do data on real-world experience compare with the trial data?	Not aware of real world data
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. If recommended, how likely is tofacitinib to be used instead of secukinumab for treatment of AS?	I believe they both have their place in the management of AS. They both have sound efficacy and safety data. Secukinumab has long term and real world data giving clinicans confidence in prescribing. Tofactinib as it is an oral agent, I believe will be a drug that patients will be keen to be considered.

27. Would you expect any differences in adherence to tofacitinib compared to secukinumab due to it being orally administered?	no
28. Would you expect tofacitinib to have a different adverse event profile to secukinumab in the population it will be used in?	no
29. Would you expect tofacitinib to maintain the efficacy seen in the A3921119 and A3921120 trials in the longer term?	yes

PART 2 -Key messages
30. In up to 5 sentences, please summarise the key messages of your statement: • Significant unmet need exists for patients with AS, due to failure of response or loss of response to existing therapies and this technology offers an additional therapeutic option • First of its kind oral small molecule targeted therapy for AS • Provides convenience for patients as simple administration compared to injections

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Thursday 19 May 2022**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	**X** a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? X a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	National Axial Spondyloarthritis Society
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement X ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	**X** I am drawing from personal experience. **X** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Discussion with members of my local NASS branch (Cambridge) ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference **x** I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference. The teleconference was held on the same day and time as the deadline! ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	I live with Axial Spondyloarthritis. 3 years ago it was classified as non-radiographic, but was diagnosed via clinical history and MRI. Since I've not had scans or xrays since, it is not possible to say if I have progressed to Ankylosing Spondylitis. I chair the Cambridge Branch of NASS, and regularly talk with others who have both Ankylosing Spondylitis, and Non-Radiographic Axial Spondyloarthritis. Every day my life is affected by my condition, both physically and mentally. In the years leading up to diagnosis I had spells where my condition was quiet, and others where it was more active, but in that time I required an early hip replacement due to damage caused by inflammatory arthritis.

	Since my diagnosis, I have been on a rollercoaster, trying to find the best combination of treatments that I can not only tolerate, but which impact sufficiently on my condition. It has taken 3 years to be in a better place, and no one is sure how long that will last, and I still vary from day to day. Frequent night time waking due to pain and stiffness has one of the biggest impacts on my mood, energy, and ability to cope. A good night at the moment is still getting up 2 or 3 times. A reasonable night in my book would be 4 or 5 times. A bad night might be 10+ times a night. More than two or three of those in succession have a hugely detrimental impact on my ability to work and function. To put it into context, until my most recent treatment regime, I would have maybe 1 good night a month. I left my full time job in London some 6 years ago as I was struggling with pain, and overload on top of commuting and looking after my children. I was diagnosed with anxiety and depression, but taking a year out, medication to help, a lot of exercise and physio, and CBT all helped. I am lucky now to work as a freelancer, from home, mainly working for a global health organisation where I can vary my hours to manage fatigue and pain. I work on average 3 days a week, but spread out over 5 days. Every day I have to be careful what I eat and drink, and what I do for exercise (walking, stretching, hydrotherapy, specialist exercise classes, but not too much of any one activity). Doing the wrong thing triggers flares. I can no longer go to a supermarket to do a big shop, or clean my own home, and I have to juggle what activities I need to do with what I want to do, so that I can manage. I cannot sit for long without becoming very stiff. I also attend a private physio once a month. I can have pain almost anywhere, but of particular issue are my SI joints, neck, and enthesitis in hands, and feet – I have had Plantar Fasciitis and Achilles Tendinitis for over 2 years. I can no longer perform as a singer (I was trained as one) due to the challenges of standing as a soloist or in a choir for performances). I also have to deal with psoriasis flares on my hands and feet. For a period of around 2 years I was very prone to falls (about 5 or 6 a year), on one occasion resulting in

	significant facial/dental injury), and on another, cracked ribs. So the impact of the disease is very significant. In terms of my treatment history I have tried the following drugs: I hope it highlights the challenging journey of trying to find the best treatment regime, that is common for many - Ibuprofen (pre-diagnosis, in relation to a knee injury that did not heal for 6 months, but this gave me chemical gastritis) - Naproxen (on diagnosis) however this did not help sufficiently (3 months) - Meloxicam (after the Naproxen). This worked better but was not sufficient to control the pain (approx. 2 years) - Adulimumab. I spent a year on this drug, even though it really was not helping much at all, and caused significant side effects, including frequent infections, and in the early days overwhelming fatigue which contributed to my major fall. However, due to Rheumatology appointment timings, and the start of the pandemic, I was not switched to a new drug until 12 months after I started it. I was on Meloxicam during this time - Secukinumab. The best response I have ever had to drug treatment was on this drug, together with Meloxicam during the loading dose stage. I was a completely different person. However the monthly dose of 150mg was not sufficient. That was increased to 300mg. At this point I developed a gut reaction that was gastritis once again and I had to stop Meloxicam. This led to a deterioration. - Celecoxib. Six months without NSAIDS was detrimental to my condition, even whilst on Secukinumab, so Rheumatology agreed to try Celecoxib as well, however despite all the stomach protectors my gastritis returned quickly. - Methotrexate. I am now on methotrexate with Secukinumab and after 3 months feel good progress is being made, though as yet my liver function

	has not quite settled down. I am more flexible, sleep better, have more energy (generally). Still prone to some stiffness and pain, but quite different from before. - I will be reviewed in a couple of months to determine whether or not the Secukinumab is working well enough and whether or not I need to change biologic again
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There are a number of medical treatments available. Whilst there currently is guidance on what to try first (NSAIDs, then Adulimumab) it can take a while to get through these if they are not effective, during which time people can experience significant disease progression. Overall, I think the more options there are the better, as finding the treatment that works for any particular patient (or combination of treatments) takes time and is affected by so many factors. I do have a concern that in some areas only three biologics can be used. If a treatment is licensed and approved by NICE then it should not be rationed by local areas. All the current biologics are injections, which once people get used to them are ok, but the option to have a tablet form may be welcomed particularly by those who are needle-phobic, or who find the fridge storage of the injections tricky, for example if travelling, or in shared accommodation. In talking with others, I hear a similar story of trial and error in finding the right drug, and the need for hope that something will work. This is why it is important to have different drug mechanisms as options (anti TNF, IL17A and 23 inhibitors, and now hopefully JAK inhibitors). There is a lot of initial fear over injections and side effects or risks, but those usually dissipate once therapy has started if it is effective.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how	Disadvantages of current treatments are that the biologics are injectable. For some this is a scary prospect and actively puts them off trying them, in addition to fear over side effects. However, for those who get good relief from their biologics, you will hear people describe it as ‘transformational’, and life-changing.

the treatment is given or taken, side effects of treatment etc) please describe these	Storage can be an issue – having to refrigerate injections means that around holiday times or trips for work, it can be hard to arrange safe transportation, or patients have to miss doses with negative effects. It may also be an issue for people in shared accommodation, where they cannot rely on others to make sure the injections are stored in the optimum conditions, and who do not wish to have overt signs of their medical condition on display to others. Some of the current treatments may have particular side effect profiles that make them unusable for some patients. Secukinumab was selected for me, not just because I failed my adalimumab, but we discussed the benefits of prevention of uveitis, and the risk of bowel issues. I am blind in one eye, and do all I can to prevent damage to my good eye. Whilst I have not had uveitis, my mother had repeated bouts of it, so I am aware I may be prone, given her side of the family has a strong history of inflammatory arthritis/psoriasis. Being immunosuppressed is a big issue for patients, but from my experience the level to which I'm prone to infection seems to have lowered since I changed biologic. Having a choice of treatments, may mean that people can find one that suits them better.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	The advantages of the proposed treatment are that because it involves a new mechanism of action it may benefit others who have previously not been able to find any relief. The fact that it is an oral tablet taken daily may mean it is easier for patients to comply, and the storage issue is also an important factor. It does not require special conditions. Brain fog can be a significant issue, so trying to remember when your injection is due can be an issue. Although it is easy to say I take it on the '15th of the month' for example, that schedule invariably gets disrupted if there are infections, surgeries, etc.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	9b. For me the most important factor is the increased choice of treatments. My experience has shown me that side effects or pre-existing conditions may well limit choice if one particular treatment is not effective or stops working. 9c. This new treatment would overcome the issues of storage and having to self-inject.
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	If I were offered this treatment I would seriously consider it, if it might work better than my current combination, but I would want to have a serious discussion about the risks of clots which are flagged in the side effects, and other possible risks which appear to be different to some of the current biologics. It is also not suitable for people over the age of 65. Whilst most AS patients are younger, there are a significant number of us who are older, either diagnosed late, or who have been struggling on treatments for years. If I went onto it at the age of 58, would I have to come off at the age of 65? If it were working well, that would be an incredibly hard thing to do. The only disadvantage I can think of applies to the current ones as well. There is no way of knowing a patient's likely reaction to treatment. The sooner some sort of biomarker can be developed to determine the BEST option for an individual patient the better, as a lot of time can pass before effective solutions are found, and in that time patients are increasingly disabled and at risk of exclusion from work and social activities.

Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Students or others who live in shared accommodation may benefit – having to share fridges with others, and have such an obvious statement of 'ill-health' visible to others can be quite stigmatising, so a tablet form would be welcomed. This would also apply to those who are needle-phobic or find the physical act of self-injecting difficult. It may also be more appealing to people who care about the amount of waste that injections/packaging/sharps bins Older people (over 65s) may miss out, and those who may also be at risk of clots. This might be pertinent for people who have had COVID recently.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	The danger in not allowing this treatment is that some people who do not respond well to other treatments or can no longer take them due to waning efficacy or side effects are left without options, rendering them with an increased chance of outcomes such as disability/chronic pain/ inability to work or socialise, thus marginalising them even further. Providing this treatment may prevent people deteriorating to the point that they become disabled (registered or otherwise).

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 3 -Key messages

14. In up to 5 sentences, please summarise the key messages of your statement:

- It is important to have a range of treatments, and new mechanisms of action to treat this disease, as for most people there is not a simple 'treatment journey'
- Being able to choose an oral medication that does not need special storage, rather than one that is self-injected and has to be stored in a fridge is important.
- Treatment for Axial Spondyloarthritis/Ankylosing Spondylitis often entails trialling different drugs, and different combinations of drugs to find what works best for an individual patient. It would be easier if tests could determine what will work best, but until then it is trial and error. That takes time and have a detrimental effect on mobility/ability to function and mental health.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

NICE National Institute for Health and Care Excellence

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team). Please return this form by **5pm** on **Thursday 19 May 2022.**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide.
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Tofacitinib for treating active ankylosing spondylitis [ID3865]

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	a patient with this condition? YES a patient with experience of the treatment being evaluated? a carer of a patient with this condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation.	National Axial Spondyloarthritis Society (NASS)

4. Has your nominating organisation provided a submission? Please tick all options that apply.	No, (please review all the questions below and provide answers where possible) Yes, my nominating organisation has provided a submission I agree with it and **do not wish to** complete a patient expert statement Yes, I authored / was a contributor to my nominating organisations submission I agree with it and **do not wish to** complete this statement I agree with it and **will be** completing YES
5. How did you gather the information included in your statement? (please tick all that apply)	I am drawing from personal experience. YES I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I have completed part 2 of the statement **after attending** the expert engagement teleconference I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference I have not completed part 2 of the statement

Living with the condition

6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	For me, living with this invisible condition and experiencing the associated chronic pain in those years before diagnoses was terrifying and I felt it robbed me of my teenage years and early twenties. My journey to diagnosis took too many years. I first noticed an issue when I was 13. I was diagnosed aged 36. My symptoms have included: Chronic fatigue, Extreme stiffness, always feeling cold, Lower back pain, Swollen joints, Chest pains, Unexplained bruising and Brain fog. Light and sound sensitivity, Heel pain, Weak hands, Poor sleep, Restless legs and Jaw pain. As a teenage / young person I was worried about my own sanity. Not being believed, then having surgery that did not solve the issue, and the symptoms mounting up, all led me to suffer with depression, fears for the future and phobias. I literally slept my early 20's away. My career was dictated by the pain, fatigue and stiffness. Thankfully my employer was very accommodating of my chronic pain and fatigue. It was devastating to watch friends socialising and having fun whilst I could barely walk or stay awake. Friendships suffered. I couldn't participate in social events and other 20 somethings just couldn't understand my invisible disease. I got a reputation for being unreliable, as I often cancelled at the last minute and for being boring as alcohol didn't mix with my medication. I stopped going out and I became isolated. Over the years I was seen by 3 different rheumatologists who diagnosed me with different things including a false diagnosis of Lupus having spent 3 months worrying about it. Despite living with chronic lower back, rib and hip pain I experienced a successful pregnancy with my first child but when my son was a few months old I had bilateral

	carpal tunnel syndrome and had surgery then later I had to have my basal thumb joint replaced too. This led to me losing my independence and I was suffering with unbearable lower back stiffness. I struggled to take part in daily activities. This involved my self-care and I felt like a helpless child as my parents were looking after the children and me, doing my housework and shopping for me. Being the parent, I couldn't be at the time. The dynamic changed from parents to carers, and it's never really gone back. This has impacted their life greatly as they changed their working hours to help me. I feel so much guilt for that. It has not been easy for them, my husband or my children. My mental health suffered. The fatigue was too much. The chronic pain interfered with my sons bath time, bed time and play time. Bending over, sitting on the floor, all lead to me getting 'stuck' and having pain. Chronic pain messes with your mind and rational thinking. I experience a traumatic pregnancy with my second child a daughter who was born 15 weeks premature. My body did not cope well to this situation at all. I came out in massive blisters, like burns. The next three years were extremely hard mentally and physically. Now I was in pain and looking after a child aged 3 and a child who needed all my attention. As well as being on high fight/flight/freeze alert. It was tiring. Having chronic pain for all those years caused me to clench my jaw and so with this new added stress I had issues with my temporomandibular joint. I clenched all the time. I needed to start wearing a mouth guard. I have an amazingly supportive husband but at times our relationship felt distant as the pain and stiffness meant I didn't feel comfortable with intimacy as I feared the pain.

	Living with AS has led to a loss of sex drive and I have experienced suicidal thoughts. Pain interrupted my thinking and living with chronic pain and stiffness made me worry whether it would ever end. Over time I became agoraphobic, and had OCD tendencies, panic attacks started, and my world became so small. I was diagnosed with PTSD and General Anxiety Disorder. Catastrophising became my normal response as the world was full of danger and worry. Depression meant I had little appetite and I had difficulties making decisions and I felt worthless Aged 36 I finally received my diagnosis: Bilateral Sacroillitis - Ankylosing Spondylitis. Some days I can get up and shower and get ready for the day and all my energy is the depleted and I have nothing left to give. Other days I can get through my morning routine quickly and do many other tasks too. This is exciting and leads to me doing too much. Resulting in a tired and depleted day the following day. It's a cycle that is hard to break. You just what to feel normal. I have used aids such as a neck brace, back brace, wrist supports, knee supports, Kinestology tapes , crutches and walking sticks just to help me function. I have needed help to physically get out of bed taking my husband hours on some occasions to slowly move me.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Please see question 8 for my experience of current treatments.
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Methotrexate - induced severe nausea and a rash Sulphasalazine - gave me an allergic reaction Naproxen - upset my stomach Amitriptyline - induced brain fog and anxiety Humira (Adalimumab - not a biosimilar) gave me extra anxiety as the items needed to be refrigerated and self administered. I would spend the morning preparing for myself to inject. I would wake up feeling nauseas, with a blotchy rash and pounding heart just because it was 'injection day'. For someone already suffering with GAD and PTSD this was a very stressful situation. But the Humira was working - and then I was diagnosed with Malignant Melanoma and all the medication was stopped. I do belong to forums where others using these drugs have positive experiences so I feel that a patients mental state when prescribed the medication can greatly affect the efficacy.

Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	Less disruption to a persons life as will not need to wait in to sign for the medication from the delivery company. They will be able to continue working. No stress or anxiety regarding refrigerating the drugs upon delivery. Freedom the travel around the UK and the world with the medication.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	I think the most important advantage is not having to refrigerate the drug as this will lower anxiety levels.
9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	

Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Not that I am aware of.
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think people who live in shared accommodation with shared kitchen facilities would benefit from this drug being in tablet form. It takes away worry that someone could take your medication out of the fridge by mistake and it become unusable. Patients who have arthritis in their hands will benefit from nothing to use a syringe to administer their medication. Patients who have needle phobias would benefit too.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	Not that I am aware of.

real and https://www.gov.uk/discrimination-your-rights.	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 3 -Key messages
14. In up to 5 sentences, please summarise the key messages of your statement: • Ankylosing Spondylitis has the power to control every area of your life • Living with worry and fear can make the pain worse • Good Mental Health is a big factor in living well with Ankylosing Spondylitis • Sometimes the side effects of the drugs can be worse than the ailment you are trying to treat • It is possible to live well with Ankylosing Spondylitis by looking at past trauma and patterns in the way you think, healing from them and releasing them and making a positive mindset plan allowing you to move forward.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group's Report

Fast Track Appraisal – cost comparison

Tofacitinib for treating active ankylosing spondylitis [ID3865]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Mark Corbett, Research Fellow, CRD, University of York Ruth Walker, Research Fellow, CRD, University of York Sumayya Anwer, Research Fellow, CRD, University of York Lucy Beresford, Research Fellow, CRD, University of York Matthew Walton, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist/Research Fellow, CRD, University of York Han Phung, Research Fellow, CHE, University of York Marta Soares, Senior Research Fellow, CHE, University of York Claire Rothery, Senior Research Fellow, CHE, University of York Ana Duarte, Research Fellow, CHE, University of York Sofia Dias, Professor, CRD, University of York
Correspondence to	Professor Sofia Dias, CRD, University of York, York, YO10 5DD
Date completed	16/02/2022

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Declared competing interests of the authors

None.

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the talks or education sessions. More information is available at https://rheumatologyevents.org.
We are grateful to Connor Evans for proof-reading a draft version of this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Mark Corbett wrote the critique of the decision problem and clinical effectiveness and safety evidence. Ruth Walker contributed to the critique of the decision problem and safety evidence (discontinuation rates). Sumayya Anwer and Lucy Beresford contributed to the critique of the network meta-analyses. Helen Fulbright wrote the critique of the search strategies. Matthew Walton contributed to the critique of the economic evidence. Han Phung performed the validation of the models and outputs. Ana Duarte contributed to the critique of the economic evidence, conducted the economic analyses and took overall responsibility for the economic section. Marta Soares provided leadership support to the economic section early in the project and reviewed the final report. Claire Rothery contributed to the critique of the economic evidence, provided leadership support and reviewed the final report. Sofia Dias was project lead, supported the critical appraisal of the evidence and takes responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Copyright statement

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List of abbreviations

AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath AS Metrology Index
bDMARD	Biologic DMARD
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSRBR	British Society for Rheumatology Biologics Register
CFB	Change from baseline
CI	Confidence interval
CMU	Commercial Medicines Unit
CrI	Credible interval
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DIC	Deviance information criterion
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EMA	European Medicines Agency
ERG	Evidence review group
FDA	Food and Drug Administration
FE	Fixed effects
FTA	Fast track appraisal
GP	General practitioner
HCHS	Hospital & community health services
HLA-B27	Human leukocyte antigen-B27
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology appraisal
IBD	Inflammatory bowel disease
IGRA	Interferon gamma release assay
IL-17A	Interleukin 17A
ITC	Indirect treatment comparison
IV	Intravenous
JAK	Janus kinase
MA	Meta-analysis
MACE	Major adverse cardiovascular events
MCS	mental component score
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction

MTA	Multiple technology appraisal
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PsA	Psoriatic arthritis
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QFT-GIT	QuantiFERON-TB Gold-In Tube
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RE	Random effects
RoB	Risk of bias
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short form health survey
SF-36v2	36-Item Short Form Survey
SmPC	Summary of product characteristics
SR	Systematic review
STA	Single technology appraisal
TB	Tuberculosis
TNF	Tumour necrosis factor
TSD	Technical Support Document
VAS	Visual analogue scale
VTE	Venous thromboembolism

EVIDENCE REVIEW GROUP REPORT: FAST TRACK APPRAISAL (FTA)

1 SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

1.1 Safety of tofacitinib

Tofacitinib carries a Medicines and Healthcare products Regulatory Agency (MHRA) safety warning, stating that unless there are no suitable treatment alternatives it should not be used in patients with cardiovascular, malignancy or other specific risk factors. This is due to an increased risk of major adverse cardiovascular events (MACE), malignancies, pulmonary embolism, deep vein thrombosis, venous thromboembolism (VTE), serious infections and all-cause mortality in at-risk patients. Based on these risk factors, estimates suggest that at least half the ankylosing spondylitis (AS) patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives. Of the remaining patients there is uncertainty about what proportion will develop risk factors in the future (e.g. starting smoking) and about whether tofacitinib might contribute to the development of some risk factors (as opposed to exacerbating existing ones). The submission safety data did not allay these concerns because long-term data in AS are not available. The safety data, therefore, do not appear to support the claim that tofacitinib's safety profile is similar to biological disease modifying anti-rheumatic drug (bDMARD) comparators.

1.2 Pathway position and comparators

Based on the safety warnings, the first-line positioning of tofacitinib in the company's submission and the use of adalimumab as a comparator does not seem appropriate and is very unlikely to reflect how tofacitinib will be used in the National Health Service (NHS). Although secukinumab and ixekizumab were subsequently added as comparators at clarification stage, clinician feedback, coupled with the MHRA safety warning, suggest that tofacitinib will likely be used as a new line of therapy in most patients. The evidence review group's (ERG's) advisers also thought that tofacitinib could sometimes displace the use of a second interleukin-17A (IL-17A) inhibitor or, very rarely, be used as a first-line treatment in needle-phobic patients.

If used as a new line of therapy (i.e. the last line of therapy), the relevant comparator would be established clinical management without bDMARDs, which is not listed in the National Institute for Health and Care Excellence (NICE) scope. Established clinical management would not be a suitable comparator for FTA as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects.

1.3 Similar effectiveness relative to selected comparators

The ERG considers non-inferiority between tofacitinib and the selected comparators plausible on the basis of the evidence presented, albeit caveated by a number of uncertainties. The company submission (CS) presented network meta-analyses (NMAs) that showed no evidence of differences between tofacitinib and adalimumab and secukinumab in bDMARD- naïve patients and between tofacitinib and secukinumab and ixekizumab in bDMARD-experienced patients.

However, these analyses were limited by failure to include all evidence on tumour necrosis factor-alpha (TNF-alpha) inhibitors, and the small number of studies with few events included in the bDMARD-experienced networks.

1.4 Similarity of costs across interventions

For comparison of treatment acquisition costs inclusive of patient access scheme (PAS) discounts for tofacitinib and comparators, please refer to the confidential appendix. Costs relating to monitoring may have been underestimated for tofacitinib, and costs relating to the treatment of adverse events (AEs) were not included. The magnitude of these costs and their relevance to tofacitinib and comparators represents a source of uncertainty. The robustness of the results of the cost-comparison analyses is further affected by the areas of uncertainty highlighted in Sections 1.5, 1.6, 1.7 and 1.8. The ERG also notes that the appropriateness of assessing the cost-effectiveness of tofacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) of tofacitinib to at least one relevant comparator.

1.5 Long-term efficacy: area of uncertainty

The cost comparison necessarily assumes that tofacitinib has similar long-term efficacy to comparators. However, no robust long-term efficacy data was presented to support the assumption of long-term maintenance of treatment response on tofacitinib. As a first-in-class treatment in this indication, the validity of assuming equivalent long-term efficacy to bDMARDs is highly uncertain.

The ERG also notes that data on long-term real-world adherence to tofacitinib were not available (see Section 1.6). Due to the short biological half-life of tofacitinib relative to bDMARDs (hours vs. weeks), adherence issues leading to missed doses of tofacitinib may have a greater impact upon continuing efficacy, with potentially important implications for maintenance of response.

1.6 Long-term discontinuation: area of uncertainty

The cost comparison necessarily assumes that tofacitinib has similar long-term discontinuation to the comparators, and treatment discontinuation due to AEs or loss of response for tofacitinib and comparators is not modelled. However, only very limited data on all-cause discontinuation were

reported for tofacitinib. As a twice-daily orally administered therapy, barriers to treatment adherence may differ compared to monthly subcutaneous (SC) injections. Furthermore, loss of efficacy over time due to adherence issues or other as yet uncharacterised reasons may lead to differences in long-term rates of discontinuation. The implications of differential rates of treatment discontinuation upon the cost-effectiveness of tofacitinib can only be explored in a full cost-utility analysis, in order to capture downstream effects on costs and health outcomes. Therefore, the potential risk to the NHS if treatment discontinuation for tofacitinib differs relative to the comparators in either direction is uncertain, as the impact on costs and health outcomes is not captured in the cost comparison.

1.7 Time horizon: area of uncertainty

The most relevant time horizon for the cost comparison analysis is unclear due to uncertainty regarding the predicted duration of treatment with tofacitinib. Both the ERG and company's base case results are sensitive to the duration of the time horizon once the confidential prices of the comparators are considered.

1.8 Modelling the impact of adverse events

The cost comparison analysis does not include the costs associated with AEs for any of the treatments under comparison. The inclusion of these costs, as requested by the ERG at the clarification stage, would have allowed exploration of the uncertainty associated with the safety issues highlighted above for patients treated with tofacitinib. While the inclusion of AE costs in the cost comparison would have been appropriate, the issue remains that potential differences in the incidence of AEs between tofacitinib and comparators cannot be accounted for within the scope of a cost comparison FTA, and would require a cost-utility analysis to capture the impact of AEs on costs, health-related quality of life (HRQoL), and the consequences of discontinuing and switching treatment.

If the long-term safety profile of tofacitinib differs to that of the comparators, this exclusion would have uncertain implications upon the relative cost-effectiveness of tofacitinib.

2 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The positioning proposed in the main CS was in line with tofacitinib's marketing authorisation, i.e. used as first or subsequent line of therapy. The company stated that there is a clear unmet need for further options in the treatment of AS. Adalimumab was the chosen comparator. However, after clarification the company presented analyses comparing tofacitinib with secukinumab in bDMARD-naïve patients and comparing tofacitinib with secukinumab and ixekizumab in bDMARD-experienced

patients, stating that this was "*for completeness and in order to remove the uncertainty around the use of tofacitinib in subsequent lines of therapy*".

2.1 Relevant decision-problem according to NHS practice and the NICE scope

Population

The ERG's clinical advisers noted that in October 2021 the MHRA issued a safety warning about tofacitinib, advising that unless there were no suitable treatment alternatives, tofacitinib should not be used in patients with any of the following risk factors: over 65 years of age, current/past smokers, VTE risk factors, cardiovascular (such as diabetes or coronary artery disease) risk factors or malignancy risk factors (see Section 3.3).[1] For the purposes of this appraisal, this safety warning[1] effectively restricts the population to a subset of the population defined in the NICE scope (i.e., those who are younger than 65 years of age, never smokers, and without VTE, cardiovascular, or malignancy risk factors), but the clinical evidence provided by the company in support of the assumption of equivalent effectiveness and safety profile of tofacitinib and comparators in the cost comparison was generated in an unrestricted population. In light of this, the ERG asked the company to comment on the representativeness of the trial populations in relation to those currently eligible for treatment, and any implications for trial effect estimates. In the point for clarification response the company said it did not anticipate this issue to substantially affect the population addressed in the appraisal or the decision problem. The company presented data on patients with at least 40% improvement in the Assessment of SpondyloArthritis International Society scale (ASAS40) showing similar efficacy in subgroups based on smoking status (and other risk factors). The ERG notes that the evidence presented is limited in terms of outcomes so does not sufficiently resolve the uncertainty on this issue. It is also unclear whether any patient characteristics are effect modifiers. The company also provided tofacitinib clinical trial and British Society for Rheumatology Biologics Register (BSRBR) data which indicated that around 25-30% of AS patients were current smokers, 16-33% were former smokers, 11-20% had hypertension and 3-5% had diabetes. Tofacitinib's summary of product characteristics (SmPC) states that it should be used with caution in patients with known risk factors for VTE regardless of indication and dosage. One of the risk factors is obesity; in pivotal study A3921120, 23% of patients had a body mass index (BMI) of $\geq 30 kg/m^2$. Estimates therefore suggest that, based on the MHRA guidance on restricted use and tofacitinib's SmPC, at least half the AS patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives, i.e. as a last line of therapy. Moreover, of the remaining patients (those not currently with risk factors for serious adverse events (SAEs)) there is uncertainty about:

- What proportion will have risk factors in the future e.g. starting smoking, development of hypertension and,

- Whether tofacitinib might be the cause of the development of some risk factors (as opposed to exacerbating existing risk factors).

This further reduces the proportion of the AS population for which first-line tofacitinib treatment is appropriate. Therefore, in terms of clinical trial evidence, the most relevant population is patients who have already taken one or more bDMARDs (rather than bDMARD-naïve patients) for whom there is limited trial evidence. Only one of the two tofacitinib trials included bDMARD-experienced patients (study A3921120) and in this study only 23% of patients had previously taken a bDMARD therapy. This limits the applicability of the tofacitinib trial populations to an NHS setting.

Comparators

Adalimumab (in biologic-naïve patients) was the only comparator considered in the CS. At the clarification stage, the ERG requested the company to comment on how the MHRA safety issues may affect the pathway position of tofacitinib in the NHS. In its response the company presented NMAs comparing tofacitinib with secukinumab in bDMARD-naïve patients and comparing tofacitinib with secukinumab and ixekizumab in bDMARD-experienced patients. The company compared the costs of secukinumab 150mg and secukinumab 300mg (for patients for whom dose is increased to 300mg according to clinical response after 16 weeks with secukinumab 150 mg). The company did not present clinical evidence to support the comparison with secukinumab 300mg (see Section 3.2.3). Secukinumab 300mg has also not been recommended by NICE.[2] Therefore, when discussing the appropriateness of secukinumab as a comparator, the ERG refers specifically to secukinumab 150mg.

The ERG asked their two clinical advisers which biologic therapies they considered to be the most frequently used for AS in the NHS, across the various patient subpopulations and subgroups. Their responses, summarised in Table 1, portray variation in practice and also illustrate the importance of considering how best to treat any extra-articular manifestations when deciding on a therapy. Generally, a TNF-alpha inhibitor would be tried first, usually followed by either a second TNF-alpha inhibitor or an IL-17A inhibitor. The ERG's advisers thought that around 95% of patients would receive a TNF-alpha inhibitor as a first-line therapy, usually adalimumab or etanercept. Both advisers also considered secukinumab to have a small market share (around 5%) as a first-line therapy, explaining that they would only use it in patients with: a high risk of tuberculosis (TB); severe skin psoriasis (Psoriasis Area and Severity Index (PASI) >10, which is rare); personal or strong family history of multiple sclerosis; or suspicion of concomitant lupus. Sometimes all the treatment options within a therapy class would be tried before moving on to a treatment with a different mode of action. This may depend on extra-articular manifestations, on whether patients achieve initial treatment responses, which are eventually lost, or on whether they fail to achieve an initial response.

The ERG's clinical advisers also commented on the anticipated use and positioning of tofacitinib. Table 1 shows that for all patients except those with inflammatory bowel disease (IBD), the ERG's clinical advisers did not foresee tofacitinib being used before the third-line of treatment and they anticipated it being used as the last-line of treatment in many patients. These positionings are based both on the level of confidence in the efficacy and safety profile of TNF-alpha inhibitors and IL-17A inhibitors and on tofacitinib safety concerns about an increased risk of MACE, malignancies, serious VTE and infections (see Section 3.3). For comparison and context, the ERG's advisers described how tofacitinib has been used in the NHS for treating other diseases in adults; although tofacitinib was recommended several years ago by NICE for treating patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), in the advisers' experience it has been used very little in practice (and seldom at first-line).

The ERG considers that, from a clinical perspective, the most relevant comparators for tofacitinib at third-line of treatment are likely to be ixekizumab and secukinumab, but notes that secukinumab has a greater market share than ixekizumab [redacted] respectively; see Table 1, CS). Since having a significant market share is one of the FTA process criteria to establish the relevant comparator, the ERG considers secukinumab to be the relevant comparator for bDMARD.-experienced patients. The ERG notes that the bDMARD market share data provided by the company (see Table 1, CS) is not reported by line of treatment. Furthermore, the methodology used to estimate the market share of these drugs in AS (see Section B.1.1.2, CS, and company reference pack) is not clearly described. Therefore, there may be uncertainty on whether these estimates are truly reflective of bDMARD use in AS.

The clinical advisers emphasised that variation in tofacitinib use would be expected (in terms of line of treatment), depending on the extent of concerns about the risk of SAEs and on how soon the use of a treatment with a new mode of action was deemed appropriate. Such judgements might be expected to vary across clinicians and by individual patient characteristics. Nevertheless, the company's choice of adalimumab, secukinumab and ixekizumab as comparators appears inappropriate for most patients, based on the MHRA guidance on tofacitinib's restricted use, uncertainties about the development of risk factors when taking tofacitinib, and the ERG's clinical advisers' opinions. In light of this, the most relevant comparator for most (though not all) patients would be established clinical management without biologics, even though this is not a listed comparator in the NICE scope.

Table 1. ERG clinical adviser opinions on comparator use and the anticipated use of tofacitinib

Subpopulation or subgroup of AS patients	ERG clinical advisers' opinions on:	
	The comparators most likely to be used	The anticipated use of tofacitinib

Biologic-naïve	Adalimumab or etanercept for most patients. In a smaller proportion of patients an IL-17A inhibitor may be considered.	Very unlikely to be used
Biologic-naïve and contraindicated for TNF-alpha inhibitors	Secukinumab or ixekizumab	Very unlikely to be used
No response to first biologic (typically TNF-alpha inhibitor)	Either try another TNF-alpha inhibitor or switch to secukinumab or ixekizumab	3rd line or later
Responded to first biologic (TNF-alpha inhibitor) but lost response later	Either try another TNF-alpha inhibitor or switch to secukinumab or ixekizumab	3rd line or later
Subgroups of patients with extra-articular manifestations (estimated prevalence in patients with AS, based on a systematic review[3])		
Patients with a history of uveitis (23%)	Adalimumab (use etanercept with caution due to risk of exacerbating uveitis). If refractory, consider another TNF-alpha inhibitor such as golimumab, infliximab or certolizumab pegol. In a small proportion of patients an IL-17A inhibitor may be considered.	3rd line or later
Patients with active uveitis (6%)	Only adalimumab is licensed for active uveitis so it is used to tackle both conditions. If refractory, consider another TNF-alpha inhibitor such as golimumab, infliximab or certolizumab pegol. In a small proportion of patients an IL-17A inhibitor may be considered.	3rd line or later
Patients with psoriasis (10%)	Use adalimumab if psoriasis is moderate-to-severe, or etanercept if psoriasis is mild. Use infliximab, certolizumab pegol or an IL-17A inhibitor if refractory.	3rd line or later
Patients with IBD (6%)	IL-17A inhibitors are not recommended. Only infliximab, golimumab and adalimumab are licensed for IBD, so are preferred to etanercept.	2nd line or later

Impact of administration preference and medication adherence on pathway position

The CS (page 27) stated that there is an unmet need for an oral therapy and that patients with other rheumatological conditions have been shown to prefer oral therapies over injectables due to ease of administration. The ERG notes that in the study cited in the CS on oral therapy preference[4] (in patients with RA) most patients (60%) had taken oral-only therapies, so many patients were expressing preferences after experiencing only one mode of administration. This limitation may also reduce the study's applicability to an AS population in which many patients have already received injectable treatments. The study found that those taking an oral-only therapy were almost nine times more likely than those on an intravenous (IV) or SC therapy to prefer oral administration. The study was also limited in that it did not record strength of preference.

The clinical advice to the ERG was that oral administration was unlikely to be an important advantage from the perspective of most AS patients, although it is very likely to be beneficial for needle-phobic patients. The ERG's advisers stated that very few patients would receive tofacitinib at the first-line of treatment as a result of being needle-phobic. In their experience, very few patients were needle-phobic, and patients who disliked needles could tolerate monthly injections. Adalimumab requires maintenance injections once every two weeks (Q2W) and secukinumab and ixekizumab are

administered monthly. Following initial training from a healthcare professional, they may be self-administered at home by the patient. The ERG's advisers thought that such comparators were unlikely to be too much more burdensome to most patients than a twice-daily oral option. Clinical advice to the ERG was also that an oral medication would unlikely be cost-saving compared to a self-administrable injectable (and often delivered cost-free within patient programmes led by companies who manufacture bDMARDs).

The ERG's clinical advisers also thought that adherence and compliance with a twice-daily tablet may possibly be problematic for some patients. For example, younger people of working age may forget to take a tablet during the day and older patients may have reduced adherence as a result of polypharmacy issues (i.e. they may have too many prescribed tablets to remember to take them all). Week 16 analysis (up to 48 weeks) of compliance with tofacitinib 5mg was reported for trial A3921120 (clinical study report (CSR) Table 14.4.1.9**)**. At 16-week follow-up, cumulative incidence of under-compliance is reported as [redacted] at 16-weeks follow-up and [redacted] at 48-weeks follow-up (Table 14.4.1.9 CSR**)**. For trial A3921119 non-compliance (<80% compliance overall) was reported as [redacted] for 5mg tofacitinib (CSR Table 14.1.7.1). In practice, clinical monitoring of adherence to tablets is also likely to be more difficult than that of adherence to biologic therapies. The ERG also notes that due to the biological half-life of tofacitinib, missed doses, treatment interruptions, and other issues leading to reduced adherence may have a greater effect upon the drug's efficacy compared to the less frequently administered SC biologics. The ERG considers this to have been inadequately explored.

The need for an oral medication option for the treatment of AS may therefore be less pressing than the CS suggests, although it will be beneficial for the few patients who are needle-phobic.

2.2 Summary of ERG's view

The first-line positioning of tofacitinib in the company's submission and the use of adalimumab as comparator does not seem appropriate and is very unlikely to reflect how tofacitinib will be used in the NHS. The addition to the submission of secukinumab and ixekizumab as comparators is welcomed, although it would appear that tofacitinib is most likely be used as a new line of therapy (or to displace a second IL-17A inhibitor). If used as a new line of therapy, as appears likely for most patients (based on clinical advice), then the relevant comparator would be established clinical management without biologics, which is not listed in the NICE scope. Established clinical management would not be a suitable comparator for FTA as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects. Furthermore, the use of tofacitinib as an additional line of therapy implies a potential impact to downstream costs and HRQoL

outcomes of managing the condition, which can only be captured by explicitly modelling subsequent lines of treatment in a cost-utility framework.

The introduction of an oral medication for treating AS is useful, although it is unlikely to change choice-of-treatment decisions for the vast majority of AS patients.

3 SUMMARY OF THE ERG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1 Systematic review

3.1.1 Search strategy

The original CS included searches to identify clinical evidence studies for adult patients with AS. A description of the searches and the search strategies were included in Appendix D of the CS (pages 10-12). In response to the ERG's clarifications, a further document was provided by the company, which included additional search strategies and clarifications. The ERG's appraisal of the searches is presented in Table 2.

Table 2. ERG Appraisal of Evidence Identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	Update Searches Missing: The update searches were not included in the original CS but were provided in the response to clarifications. Confusing Representation of Hits The total number of hits shown for each line in the search strategy varies between using: * Duplicates are removed from the search but included in the result count. ° Duplicates are removed from the search and from the result count. This suggests that de-duplication has been performed on a line-by-line basis which makes it confusing to understand the number of hits retrieved by the search strategy overall. Normally, the total hits retrieved would be stated (for each line and overall) and the combined total would then be adjusted to show the number of hits after de-duplication.
Were appropriate sources searched?	PARTLY	Limited Sources Searched A limited number of databases were searched i.e., a multifile search of two databases, Medline and Embase, conducted via ProQuest. Conference proceedings, health technology appraisal (HTA) literature sources, grey literature sources and trials registry databases were not searched for in their own right using specialised databases. This was raised at the clarification stage. Although the company response clarified that prior HTA submissions were reviewed; conference proceedings were searched for additional information; and randomised controlled trials (RCTs) published only as abstracts were not targeted for inclusion; the concern represented by the ERG in the clarification stage still stands. The original CS describes that '[a] comprehensive systematic literature search was implemented to identify all available literature…' (Appendix D, page 10) and this is inaccurate. However, in the response to clarifications the company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed.

Was the timespan of the searches appropriate?	YES	No date limits were placed on the search.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population AND Intervention AND Study Type.
Were appropriate search terms used?	PARTLY	Missing Trade Names for Drugs: Strategies are missing the biosimilars of adalimumab – Amsparity, Cyltezo, Halimatoz, Kromeya, Solymbic, Yuflyma and biosimilars of etanercept – Nepexto and Lifmior. This was raised as a clarification. The company responded that these biosimilars were not included as they are unlikely to be compared to placebo alone. Missing Terms for Condition ankylosing spondylarthritides, ankylosing spondylarthritis, ankylosing spondyloarthritides, ankylosing spondyloarthritis, bechterew disease, bechterew's disease, bechterews disease, marie struempell disease, marie-struempell disease, rheumatoid spondylitis, ankylating spondylitis, ankylopoietic spondylarthritis, ankylopoietic spondylitis, ankylosing spine, ankylosing spondilitis, ankylosing spondylarthritis, ankylosing spondylarthrosis, ankylosis spondylitis, ankylotic spondylitis, bekhterev disease, morbus bechterew, spinal ankylosis, spine ankylosis, spondylarthritis ankylopoietica, spondylarthritis ankylosans, spondylarthrosis ankylopoietica, spondylitis ankylopoetica, spondylitis ankylopoietica, spondyloarthritis ankylopoietica, vertebral ankylosis The limited coverage of terms used for the condition risks missing relevant material. However, in the response to clarifications the company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed. Lack of Subject Headings / Missing Subject Headings: It is best practice in literature searching to represent each concept through a choice of subject headings or textwords, in order to capture papers with subject headings but no abstract, as well as papers with an abstract but no subject headings. However, there are no MeSH terms or Emtree terms for any the Intervention terms represented in line number S2 despite the existence of such terms. The following are all Emtree headings which could have been used: etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, secukinumab, ustekinumab, ixekizumab, netakimab, apremilast, bimekizumab, upadacitinib, filgotinib, etoricoxib, tofacitinib. The following are MeSH headings which could have been used: Etanercept, Infliximab, Adalimumab, Certolizumab Pegol, Ustekinumab, Etoricoxib. This was raised as a clarification and the company clarified that they were looking for treatment names that were specifically referred to in the title or abstract. The company made assurances that they compared their results with those of previous NICE technology appraisals and they are not aware of any studies that were missed.
Were any search restrictions applied appropriate?	PARTLY	Publication Bias Unclear Table 1 (page 10, Appendix D) of the PICOS Framework for Structuring the Literature Search specifies that non-English language papers will be excluded. This limit does not appear in the search strategy, and it is unclear if this limit was part of the search strategy or the screening criteria. This is an important distinction as many reviews that use this exclusion criteria use it as part of the screening process only, so as not to rely on the accuracy of the metadata applied on the database. This was raised as a clarification. The company response was that non-English language papers are typically excluded from literature searches. However, it is still not clear how this exclusion was applied.
Were any search filters used validated and referenced?	UNCLEAR	Study filters may have been used to limit to RCTs, systematic reviews (SRs) or meta-analyses (MAs) in the multifile search of Medline and Embase via ProQuest. However, these are not reported or referenced in the CS.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Screening, data extraction and quality assessment methods

The systematic review methods were described in Appendix D of the CS. No details were reported about the processes of title and abstract and full-text screening (e.g. such as researchers screening independently), therefore the possibility of errors and bias affecting the selection of studies cannot be ruled out.

The bibliographic database search strategies were designed to identify all the comparator interventions listed in the NICE scope. However, at the full-text screening stage of the systematic review, studies which were not of either tofacitinib or adalimumab were excluded. It is unclear why the company adopted this approach, rather than either including studies of all eligible comparators (having searched for them) or instead searching only for studies of adalimumab and tofacitinib. Moreover, restricting the review to only one comparator (adalimumab) meant there was no flexibility to allow comparisons with other biologics, if these were considered more appropriate. This is an important limitation of the company's systematic review, given the ERG's request for comparisons of tofacitinib versus IL-17A inhibitors in biologic-experienced patients. This request was specifically based on the ERG's clinical advisers stating that it was very unlikely that patients would take tofacitinib as a first-line (or even second-line) therapy. These comparators were later included in response to clarification (see Section 3.1.3), but the company did not provide details on the processes used to identify the relevant studies or extract the data.

The CS stated that the quality assessments were undertaken using the updated version of the Cochrane risk of bias tool (RoB 2), according to the tool's full guidance document. The results from the risk of bias assessment are reported in Table 7 of the appendix C-I. Only one study, Hu et al. 2012,[5] was deemed overall to be high risk of bias, due to selection of reported results. However, no details to support the judgements were reported, which limited the transparency of the assessment results. No risk of bias assessments were carried out for the additional studies included at the clarification stage.

3.1.3 Included trials

The review included seven RCTs (covered across nine publications), all of which were placebo-controlled trials of tofacitinib or adalimumab. However, the company did not include its own large randomised safety trial (called 'ORAL Surveillance') of tofacitinib versus TNF-alpha inhibitors. Although this trial was in RA patients, its primary outcomes were AEs and its results have important implications for any adults taking tofacitinib (see Section 3.3).

3.2 Clinical effectiveness of tofacitinib

3.2.1 Methods of study A3921119 and study A3921120

Tofacitinib (5mg) was compared to placebo in two multicentre, randomised trials. Study A3921119 was a phase 2 dose-ranging trial in 103 biologic-naïve patients and study A3921120 was a phase 3 trial of 207 biologic-naïve and 62 biologic-experienced patients.

Assessments were made at 12 weeks in study A3921119 and 16 weeks in study A3921120. However, 16 weeks was the timepoint specified for the primary and secondary outcomes in the pivotal phase 3 trial (A3921120). The CSR for study A3921120 indicated that

[redacted]

The quality assessments of the two trials were reported in Table 13 of the CS with the company considering the risk of bias in both trials to be low. The ERG was able to corroborate the low risk of bias judgements for all domains (although limited method details were available on blinding). However, the CS did not include an evaluation of the applicability of the trial results. The ERG notes that a limited number of bDMARD-experienced patients were recruited to the tofacitinib trials, with evidence available for only 62 such patients from study A3921120. There is also uncertainty about what impact the presence of cardiovascular risk factors have on efficacy, especially in the longer-term (around half the trial patients have a cardiovascular risk factor which may increase the risk of an SAE). Notwithstanding these issues, the ERG's clinical advisers thought that both the trial eligibility criteria and baseline characteristics were adequately representative of patients seen in NHS practice.

3.2.2 Results of study A3921119 and study A3921120

In both studies, tofacitinib was statistically significantly more effective than placebo for all the key outcomes listed in the NICE scope. Following a clarification question the company stated that extra-articular manifestation outcomes (listed in the NICE scope) were reported as safety events and were not part of the primary or secondary endpoints of the trials. The available data on this were also presented (clarification question A8, Table 11);

[redacted]

Subgroup results

In a clarification point, the ERG requested subgroup analyses based on prior biologic use with results to be presented as risk ratios or mean differences (MDs) with 95% confidence intervals (CIs). The company did not provide risk ratios for the binary outcomes, although the results provided were limited by low numbers of patients and events in the biologic-experienced subgroup. For the continuous outcomes at 16 weeks, tofacitinib [redacted] The ERG agrees though with the company's statement that these results should be interpreted with caution as the study was not powered to detect differences in subgroups by prior biologic treatment.

Long-term efficacy

Given the different mechanism of action to bDMARDs, a key area of uncertainty is the longer-term efficacy of tofacitinib and the length of time patients may sustain a treatment response. Although some patients can develop anti-drug antibodies to bDMARDs which affects efficacy, the ERG's clinical advisers stated that, in theory, patients would not develop antibodies to Janus kinase (JAK) inhibitors (as they are small molecules). However, the ERG's advisers thought there was insufficient evidence to speculate on the long-term effectiveness of tofacitinib.

3.2.3 Network Meta-Analyses

In the main CS, the company presented NMAs to compare the relative efficacy and safety of tofacitinib to adalimumab in a bDMARD-naïve and a mixed population (including bDMARD-naïve and -experienced patients). A summary of these NMAs is provided in Section B.3.9 and additional details are included in Appendix D. In response to clarification questions, the company also provided NMAs comparing tofacitinib to secukinumab in biologic-naïve patients and to compare tofacitinib with secukinumab and ixekizumab in biologic-experienced patients. Details and results for these additional NMAs are described in the company's clarifications response. The NMAs used fixed and random-effects models with and without baseline-risk adjustments adapting methods described in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 and 3.[6, 7]

3.2.3.1 Comparison to Previous Appraisals

Previous appraisals in AS have conducted NMAs to evaluate the relative efficacy and safety of TNF-alpha inhibitors (TA383), secukinumab (TA407) and ixekizumab (TA718) compared to other available bDMARDs. The methods used for the NMAs for the tofacitinib appraisal were broadly similar to the approaches used in previous appraisals, but there were some differences.

Population

The company's approach to modelling the populations is broadly similar to the previous single technology appraisal (STA) of secukinumab and ixekizumab. In TA407 (secukinumab), the NMAs modelled a mixed and a bDMARD-naïve population. In the ixekizumab appraisal (TA718), bDMARD-naïve and -experienced patients were modelled separately and sensitivity analyses were conducted including trials where the population of interest was unclear. The trials included in the multiple technology appraisal (MTA) on TNF-alpha inhibitors (TA383) had mixed populations (with the majority of patients being bDMARD-naïve).

Time point of Assessment of Outcomes

There is large heterogeneity in the time point of assessment of initial response across the trials included in the current and previous appraisals, ranging from 10-16 weeks. In previous appraisals, ERGs have considered that this approach could introduce uncertainty into the model. It has been suggested that response rates may be higher in the trials where response is measured later, as the patients have a longer period to respond to their treatment (as discussed in TA407 and TA718).

In the tofacitinib NMAs, the time point of assessment of initial response ranged from 12-16 weeks, and outcomes were pooled across studies. Given that the SmPC for tofacitinib suggests discontinuation if there is no response by 16 weeks, and for consistency with other appraisals, the ERG considers the 16-week data to be the most appropriate when comparing tofacitinib with other treatments in NMAs. This is because this would be the time point for which, in clinical practice, a decision will typically be made to continue with current treatment, or switch to an alternative (see also Section 3.2.1).

The STAs of secukinumab (TA407) and ixekizumab (TA718) used a similar approach and pooled the different time points of response assessment from the included trials, which ranged from 12 to 16 weeks. The MTA of TNF-alpha inhibitor drugs also pooled the responses assessed at weeks 10-16.

Selection of outcomes

The tofacitinib NMAs model the most extensive number of outcomes, compared to previous appraisals, and includes the modelling of HRQoL outcomes, and the BASMI score and ASAS20 (which is not included as an outcome in ixekizumab or the MTA of the TNF-alpha inhibitors). In the

additional NMAs provided at clarification stage, the company included Ankylosing Spondylitis Disease Activity Score (ASDAS) and excluded BASMI score CFB as outcomes (Table 3).

Table 3. Outcomes included in the NMAs in the tofacitinib appraisal and previous appraisals for ankylosing spondylitis

Tofacitinib (this appraisal)	TNF-alpha inhibitors (TA383)	Ixekizumab (TA718)	Secukinumab (TA407)
ASAS20 ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB BASMI score CFB SF-36 PCS score CFB SF-36 MCS score CFB ASQoL score CFB ASDAS	BASDAI50 BASDAI score CFB BASFI score CFB	ASAS20ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB	ASAS40 BASDAI50 BASDAI score CFB BASFI score CFB

MCS: mental component score; PCS: Physical component score; SF-36: 36-Item Short Form Survey

The company present a cost-comparison analysis and argue that tofacitinib has similar efficacy, safety and quality of life (QoL) outcomes to adalimumab, secukinumab and ixekizumab for all outcomes considered relevant in previous appraisals.

Fixed/Random Effects Models

In their submission, the company selected unadjusted random effects (RE) models to compare tofacitinib to adalimumab for all outcomes due to the perceived heterogeneity in the data. However, as the difference between the deviance information criterions (DICs) for the fixed effect (FE) and RE models was less than three for all outcomes, the ERG prefers the simpler FE model instead as recommended by the NICE DSU TSD2.[6] Additionally, as there were few studies per comparison in the network for each outcome, there likely is insufficient evidence to estimate the between study heterogeneity.[8-10] In their response to clarifications, the company expressed neutrality about selecting RE models over FE and considered the results of both "informative and suitable for decision-making" as the results for both models were very similar for all outcomes. In the additional NMAs comparing tofacitinib to secukinumab and ixekizumab, the company selected the simpler FE model. Previous appraisals have also favoured FE models.

Placebo or Baseline-Adjustment

The company also explored placebo-adjusted comparisons where there was enough data available. The company present the results for the FE and RE models with baseline risk adjustment in the Appendix D in the CS. Placebo-response adjustments were also explored in previous appraisals (TA407 and TA383) but were often not appropriate due to data sparsity. The company also experienced poor convergence when fitting some placebo-adjusted models due to the low number of

studies. Including other TNF-alpha inhibitors in the network could have improved estimation of the placebo-adjusted models.

Class Effect

The MTA of TNF-alpha inhibitors for AS explored whether the data supported an assumption of a class effect across TNF-alpha inhibitors; that is, that these treatments can be assumed to be similarly effective. The class effect model was found to produce a better-fitting model compared to the models that assumed independent treatment effects, and were used in the economic model.[11] There was clinical support for this assumption and, in light of the available evidence, it was considered reasonable for decision-making purposes.

The STA of secukinumab (TA407) did not consider class effects for IL-17A inhibitors but after the technical engagement process in the ixekizumab appraisal (TA718), the company considered it reasonable to assume a class effect for all biologic treatments for axial spondyloarthritis and to assume equivalent efficacy across TNF-alpha inhibitors and IL-17A inhibitors. However, the committee deemed this to be inappropriate and concluded that a class effect had not been established for all TNF-alpha inhibitors and IL-17A inhibitors.[12]

In the original CS, tofacitinib did not consider an NMA assuming class effects for TNF-alpha inhibitors. At the clarification stage, the ERG also asked the company to comment on the plausibility of a class effect for effectiveness and safety across other JAK inhibitors (including upadacitinib and filgotinib). The company did not comment on the class effect owing to the paucity of head-to-head or indirect treatment comparisons (ITCs) for JAK inhibitors. The company also did not consider it appropriate to consider a class effect for TNF-alpha inhibitors as they did not consider that the conclusions about the efficacy of tofacitinib against adalimumab would change. The company stated that adalimumab was the only relevant TNF-alpha inhibitor because in previous appraisals committees have concluded that TNF-alpha inhibitors should be considered as a class with broadly similar, even if not completely identical, effects (TA383, TA407). However, the ERG is concerned that failure to include all the evidence on TNF-alpha inhibitors in the network and assuming that adalimumab alone can be considered to represent the average class effect is a limitation. Models previously used to model the effect of TNF-alpha inhibitors and to compare them as a class (TA383[11]) have shown that adalimumab has the lowest effect in the class when compared to placebo. Therefore, it is questionable whether a network including only adalimumab can be considered to adequately estimate the TNF-alpha inhibitor class effect, as claimed by the company. The ERG argues that excluding other TNF-alpha inhibitors from the NMA will underestimate the effectiveness of TNF-alpha inhibitors as a class and increase the uncertainty in the estimates, favouring tofacitinib.

3.2.3.2 Studies included in the NMA

Initially, the company only included studies comparing tofacitinib or adalimumab in their network. Studies comparing secukinumab and ixekizumab were also included after the clarification stage.

The ERG also requested that an expanded network including all evidence on TNF-alpha inhibitors be considered but this was not done by the company. Including other TNF-alpha inhibitors such as etanercept, certolizumab pegol, golimumab, or infliximab in the network would have allowed for a class effect model to be used which would generate more robust estimates by allowing information to be borrowed from other treatments within the same class. The reasons provided by the company for this refusal did not mitigate any of the points made by the ERG in Section 3.2.3.1.

Although the company states that NMAs were conducted on two sub-populations based on previous biologic experience: (i) treatment-naïve patients, and (ii) a mixed population, it is important to note that the evidence available for an NMA of a mixed population is very limited. All adalimumab trials were conducted on treatment-naïve patients, while only one trial for tofacitinib (A3921120) included patients with prior biologic experience (only 62 patients with prior biologic experience were recruited). The ERG notes that the NMA carried out on the mixed population is not representative of a truly mixed population, given that all adalimumab evidence is on naïve patients and only a small proportion of the evidence on tofacitinib is on biologic-experienced patients.

All of the adalimumab trials were included in NICE TA383 except COAST-V which was published after TA383. In response to clarification question A13, the company also included evidence on four additional trials comparing secukinumab and ixekizumab to placebo in additional NMAs for the bDMARD-naïve and -experienced subpopulations. A list of the studies included in each NMA for adalimumab, secukinumab, and ixekizumab are presented in Table 11, in Appendix 1. There were two distinct networks for the bDMARD-naïve population and separate NMAs were conducted: one comparing tofacitinib to adalimumab, and the second comparing tofacitinib to secukinumab, instead of combining both networks and conducting a single NMA to compare the 3 interventions. Given the evidence available, where there are no head-to-head trials comparing adalimumab to secukinumab, the results from the two separate NMAs will be the same as if a single NMA, when the FE model is selected.

Subgroup data from MEASURE 2, MEASURE 4, and MEASURE 5 were included in NMAs for bDMARD-naïve and bDMARD-experienced populations. The COAST-W study only provided evidence on ixekizumab for a biologic-experienced population.

3.2.3.3 Potential Causes of Heterogeneity in the NMAs

Due to the limited number of studies included in the NMAs, the level of heterogeneity present in each network could not be reliably estimated for all outcomes. In addition, the structure of the networks for all outcomes means that there is no potential for detecting inconsistency as there is no independent, indirect evidence for any of the comparisons (loops are formed of multi-arm trials only).[13]

The company considers the trials included in the NMAs comparing the efficacy of tofacitinib against adalimumab to be relatively homogenous. The eligibility criteria of the included studies were similar, with all studies recruiting participants with BASDAI scores ≥4, who had failed either a non-steroidal anti-inflammatory drug (NSAID) or DMARD previously. The only exception was one tofacitinib trial which included patients who had previously received a TNF-alpha inhibitor (A3921120). Patients who were bDMARD-experienced in the A3921120 trial were excluded from the NMAs of biologic-naïve patients, but were included in the NMA of the mixed population, and were analysed separately in the additional NMAs comparing tofacitinib to the IL-17A inhibitors. The company do not comment on the similarity of the trials included in their additional NMAs comparing tofacitinib against secukinumab and ixekizumab at the clarification stage. The eligibility criteria of the included studies was comparable, with all trials recruiting participants ≥18 years old with active AS defined as BASDAI ≥4, and spinal pain of over 4cm on a 10cm visual analogue scale (VAS), who had an inadequate response or intolerance to NSAIDs. MEASURE 5 also includes back pain score over ≥40 mm on a 100 mm VAS. The ERG considers that the trials included in the additional NMAs to be relatively homogenous. With the exception of MEASURE-5,[14] (which was published after the ixekizumab appraisal in May 2020) all studies have been included in previous appraisals.

The definition of outcomes across the trials included in the networks are generally consistent and is unlikely to contribute to the heterogeneity.

The company provide data regarding the baseline characteristics of the studies included in the NMA of tofacitinib and adalimumab (Table 9, Appendix D of the CS) and notes that studies are similar, with the exception of Hu (2012),[5] which the company excluded from the NMAs. In Appendix D of the CS, the company note that few baseline and disease characteristics were reported for the Hu (2012) trial of adalimumab. However, the ERG notes that C-reactive protein (CRP) levels, BASDAI and BASFI scores, were reported in TA383[5, 11] where this study was included in the NMAs. The ERG also believe that the population in the Huang (2014)[15] trial is slightly different from the other included studies as patients are considerably younger, have lower BASFI scores and higher levels of CRP at baseline scores, and were more likely to be human leukocyte antigen-B27 (HLA-B27) positive compared to the other trials.[11] These characteristics are known to be predictors of response for patients with AS.[16] Given that the Huang trial is relatively large (n = 344), it could have an impact on the results.

For the additional models comparing tofacitinib against secukinumab and ixekizumab presented at clarification, the company did not provide an overview of the baseline characteristics of each included study. Overall, the baseline characteristics are relatively homogenous across the trials, although some of the baseline characteristics are not reported separately for bDMARD-naïve and -experienced patients in the MEASURE 4 and 5 trials. The time since diagnosis was lower in the MEASURE 5 (secukinumab at 150mg) and in the A3921120 (tofacitinib) trial. The company do not provide a standard deviation around the mean for the time since diagnosis in the A3921120 trial, so it is difficult to quantify the extent of heterogeneity in this variable for the patients included in the trial. The proportion of participants who were male is higher in the A3921120 and MEASURE 5 trials compared to the other studies included in the networks, which is a predictor of response in patients with AS.[16] Finally, patients in the MEASURE 5 study were considerably younger compared to patients included in the other trials. Given that trials of both tofacitinib and secukinumab have patients with baseline characteristics that are known to be predictors of response (including age and proportion of participants that were male), there is uncertainty surrounding the impact that these differences may have on the network, and whether it biases one treatment over the other. However, in previous appraisals it was accepted that studies could still be pooled in NMAs.

The time point of assessment of response is relatively similar across the trials included in the NMAs in the original CS. COAST-V (adalimumab) and A3921120 (tofacitinib) have assessment at 16 weeks as do the ixekizumab and secukinumab trials. The time point of assessment of response could impact results as participants are more likely to respond if the initial assessment of response is later.[17, 18] However, the time points used agree with previous appraisals (see Section 3.2.3.1) where it had a minimal impact on heterogeneity.

3.2.3.4 Results of the NMAs presented in the company submission

bDMARD-naïve population

Efficacy outcomes

Table 4 reports the results of the models preferred by the ERG for the efficacy outcomes. Credible intervals (CrIs) for all estimates included the null effect, therefore there was insufficient evidence to suggest a difference in treatment effects for tofacitinib compared to adalimumab or secukinumab. Forest plots comparing tofacitinib and adalimumab provided by the company in their response to clarification demonstrated that results are similar, irrespective of the final model selected.

Table 4. Results of ERG-preferred models for efficacy outcomes (bDMARD-naïve patients)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab (Loading Dose)**

OR (95% CrI)[a]						
ASAS20	6	FE	[redacted]	5	FE	[redacted]
ASAS40	6	FE	[redacted]	5	FE	[redacted]
BASDAI 50	4	FE	[redacted]	N/A	N/A	N/A
MD (95% CrI)[b]						
BASDAI CFB	6	FE*	[redacted]	5	FE	[redacted]
BASFI CFB	5	FE	[redacted]	N/A	N/A	N/A
BASMI CFB	5	FE	[redacted]	Outcome was not reported in the NMA		
ASDAS	Outcome was not reported in the NMA			N/A	N/A	N/A

[a] null effect is 1; [b] null effect is zero. N/A: This NMA was not conducted as there was no evidence available for this comparison. * The FE baseline-adjusted model had a smaller DIC (FE: 11.079, FE baseline-risk-Adjusted: 5.563).
Abbreviations: CFB: change from baseline, CrI: credible interval, DIC: deviance information criterion, FE: fixed effect, MD: mean difference, NMA: network meta-analysis, OR: odds ratio.

Quality of life outcomes

Table 5 reports the results for the models preferred by the ERG for QoL outcomes for the comparisons of tofacitinib to adalimumab and secukinumab. Only FE models could be fit for the Ankylosing spondylitis quality of life (ASQoL) CFB outcome due to the low number of studies in both networks.

CrIs for the estimates of all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in QoL between tofacitinib and adalimumab and secukinumab. Results for the only QoL outcome for which the baseline-risk adjusted model was fit, 36-Item Short Form Survey (SF-36v2) mental component score (MCS) CFB (for the tofacitinib vs. adalimumab comparison), were consistent with the unadjusted model. Forest plots comparing tofacitinib to adalimumab provided by the company in their response to clarifications demonstrated that the results would be similar, irrespective of the final model selected.

Table 5. Results of ERG-preferred unadjusted models for QoL outcomes (bDMARD-naïve patients)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab (Loading Dose)**
MD (95% CrI)[a]						
ASQoL CFB	3	FE*	[redacted]	5	FE*	[redacted]
SF-36v2 PCS CFB	5	FE	[redacted]	5	FE BL-adj*	[redacted]
SF-36v2 MCS CFB	4	FE**	[redacted]	Outcome was not reported		

[a] null effect is 0. * RE analysis not conducted due to poor convergence. ** The baseline-risk adjusted models for this NMA did not converge.
Abbreviations: BL-Adj: baseline-risk adjusted, CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, NMA: network meta-analysis, OR: odds ratio.

Adverse event outcomes

No NMAs of AEs were conducted on a bDMARD-naïve population as there was no subgroup data available based on prior biologic-experience. NMAs on AEs were conducted for mixed population; the results are reported in Section 3.3.

bDMARD-experienced population

Efficacy outcomes

Table 6 reports the results of the models preferred by the company and the ERG for the efficacy outcomes. Due to the low number of studies the company did not fit baseline-risk adjusted models for any of the outcomes. CrIs for the estimates for all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in treatment effects for tofacitinib compared to secukinumab and ixekizumab. The CrIs for the odds ratios estimated for ASAS20, ASAS40 and BASDAI50 were very wide, reflecting large uncertainty in the estimates.

Table 6. Results of ERG-preferred models for efficacy outcomes (bDMARD-experienced patients)

Outcome	Number of Studies	Selected Model	Tofacitinib vs. Secukinumab (Loading Dose)	Tofacitinib vs. Ixekizumab
			OR (95% CrI)[a]	
ASAS20	5	FE	[redacted]	[redacted]
ASAS40	5	FE	[redacted]	[redacted]
BASDAI 50	2	FE	[redacted]	[redacted]
			MD (95% CrI)[b]	
BASDAI CFB	5	FE	[redacted]	[redacted]
BASFI CFB	2	FE	[redacted]	[redacted]
ASDAS CFB	2	FE	[redacted]	[redacted]

[a] null effect is 1; [b] null effect is zero. N/A: There was no evidence for secukinumab for this comparison.
Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference, OR: odds ratio.

Quality of life outcomes

The results of the models preferred by the company and the ERG are presented in Table 7. As COAST-W did not report data for ASQoL, the NMA for the outcome only compared tofacitinib to secukinumab. The company only fit unadjusted FE models for both outcomes, due to the sparsity of the studies. CrIs for the estimates for all outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in QoL between tofacitinib and secukinumab and ixekizumab.

Table 7. Results of ERG-preferred unadjusted models for QoL outcomes (bDMARD-experienced patients)

Outcome	Number of Studies	Selected Model	Tofacitinib vs. Secukinumab	Tofacitinib vs. Ixekizumab
			MD (95% CrI)[a]	
ASQoL CFB	4	FE	[redacted]	[redacted]

SF-36v2 PCS CFB	5	FE		[redacted]		[redacted]

[a] null effect is 0. N/A: There was no evidence for ixekizumab for this comparison.

Abbreviations: CFB: change from baseline, CrI: credible interval, FE: fixed effect, MD: mean difference.

Adverse event outcomes

No NMAs of AEs were conducted on a bDMARD-experienced population as there was no subgroup data available based on prior biologic-experience. NMAs on AEs were conducted for mixed population, the results are reported in Section 3.3.

Mixed population

The company included NMAs for efficacy and QoL on a mixed population for the comparison of tofacitinib with adalimumab in the CS. These are not reported here, due to concerns that results for the mixed populations are based mainly on treatment-naïve patients (Section 3.2.3.2). NMAs carried out for AEs in a mixed population are discussed in Section 3.3.3.

3.3 Safety of tofacitinib

3.3.1 Safety evidence in AS and other indications

The CS (page 100) reported that tofacitinib "*has an established safety profile in other indications…*" and that it also "*has a comparable safety profile to adalimumab when evaluating safety during the randomised, placebo-controlled period in an AS population*" (page 88). Although the number of SAEs were low and balanced across groups in the two tofacitinib trials in AS patients, the ERG's clinical advisers alerted the ERG to ongoing concerns about the safety of tofacitinib. The MHRA issued safety updates in 2020 and 2021 warning that, unless there are no suitable treatment alternatives, tofacitinib should not be used in patients with any of the following risk factors: being over 65 years of age, current or past smokers, VTE risk factors, cardiovascular (such as diabetes or coronary artery disease) risk factors or malignancy risk factors.[1, 19] In addition to the MHRA warning, the U.S. Food and Drug Administration (FDA) required revisions to the Boxed Warning, the FDA's most prominent warning, for tofacitinib, baricitinib and upadacitinib to include information about the risks of serious heart-related events, cancer, blood clots, and death.[20] The FDA considers that all JAK inhibitors may pose similar safety risks.

'ORAL Surveillance' randomised safety trial

These warnings came as a result of RCT data showing an increased risk of MACE, malignancies, pulmonary embolism, deep vein thrombosis, VTE, serious infections and all-cause mortality in these at-risk patients. This important safety issue was not mentioned in the company's submission. The study cited by the MHRA was the randomised 'ORAL Surveillance' phase 4 (post-marketing) safety trial comparing tofacitinib (5mg or 10mg) with TNF-alpha inhibitors (etanercept 50mg every week

and adalimumab 40mg every other week) for safety outcomes in 4372 patients with RA, aged 50 years or older with at least one additional cardiovascular risk factor (defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction (MI), cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations). The co-primary endpoints were non-inferiority of tofacitinib compared to TNF-alpha inhibitors with respect to MACE and malignancies. Patients were followed up for a minimum of three years and the maximum duration of follow-up was six years. Although the trial results have yet to be published in a peer-reviewed journal, they have been posted on the study's clinicaltrials.gov record.[21] Tofacitinib failed to show non-inferiority compared to TNF-alpha inhibitors for both MACE and malignancies with the upper limit of the 95% CI exceeding the non-inferiority margin of 1.8 for both outcomes (hazard ratio (HR) 1.33, 95% CI: 0.91 to 1.94 for MACE and HR 1.48, 95% CI: 1.04 to 2.09 for malignancies). The rates of all-cause mortality were 3.37% for tofacitinib 5mg, 4.53% for tofacitinib 10mg and 2.62% for TNF-alpha inhibitors. The European Medicines Agency (EMA) reported HRs by dose. With tofacitinib 5mg as comparator the results were: MACE, HR 1.24 (95% CI: 0.81 to 1.91); Non-fatal MI HR 2.32 (95% CI: 1.02 to 5.30) and malignancies HR 1.47 (95% CI: 1.00 to 2.18). There were no fatal MIs in patients taking tofacitinib 5mg.[22]

These findings demonstrate the value of conducting a long-term, direct, randomised comparison of treatments on safety outcomes. Prior to this study's results, a study of pooled data from 7061 patients with RA who had received tofacitinib for a median of 3.1 years[23] appeared to show that (with the exception of herpes zoster) rates of tofacitinib safety events were both stable over time and generally similar to biologics.

The ERG asked clarification questions about this issue, including asking for a summary of the tofacitinib safety data relating to the increased risk of the aforementioned SAEs and all-cause mortality, and how they compare with data for TNF-alpha inhibitors. The company responded by stating that analyses of data from PsA, AS, psoriasis and ulcerative colitis populations, as well as in the non-cardiovascular risk RA population, have not shown an increased risk for tofacitinib therapy versus TNF-alpha inhibitors for MACE and malignancy. The ERG notes that most of the data presented by the company focused on differences in incidence rates across diseases, rather than comparisons with TNF-alpha inhibitors. The one study which did compare tofacitinib with TNF-alpha inhibitors was a non-randomised comparison in RA patients which reported similarities in MACE, malignancy, death, and VTE.[24] Given that this study is in RA patients (like the ORAL Surveillance

RCT) and is non-randomised, the ERG does not see this as evidence to allay concerns about the safety of tofacitinib.

The ORAL Surveillance safety trial was conducted in older patients who had at least one additional cardiovascular risk factor. It is uncertain what the safety risks are in younger patients without cardiovascular risk factors. It is also uncertain whether tofacitinib exacerbates pre-existing risk factors for developing the SAEs listed by the MHRA, or is the cause of a new risk factor (or both).

3.3.2 Tofacitinib discontinuation rates

Discontinuation of tofacitinib due to AEs is reported for A3921119 study as [redacted] at 12 weeks follow-up for patients taking 5mg tofacitinib (Table 27 of the CSR). For A3921120 data are reported at 16 weeks and up to 48 weeks follow up as [redacted] and [redacted] respectively for patients taking 5mg tofacitinib (Table 41 of the CSR). No longer-term data on discontinuation due to AEs are available for either clinical trial and therefore, this remains uncertain. Longer term data from an open-label study (ORAL Sequel long-term extension[25]) of tofacitinib (5mg and 10mg) for RA (including 4481 patients followed up to 114 weeks), suggests this could be notably higher, with 28% of patients discontinuing tofacitinib 5mg due to an AE. Furthermore, randomised data from a clinical trial (ORAL surveillance)[21] of tofacitinib (5mg or 10mg) or TNF-alpha inhibitors for RA (including 4372 patients followed up for a minimum of three years and a maximum of 72 weeks) reports permanent discontinuation rates due to AEs of 14.4% for patients taking tofacitinib 5mg and 14.5% for patients taking a TNF-alpha inhibitor (adalimumab or etanercept). Discontinuation due to lack of efficacy is reported only for the A3921120 study at 16 weeks and at 48 weeks follow-up, as [redacted] respectively (Table 14.1.1.2.2 of CSR). Longer-term data on discontinuation due to lack of efficacy are not available.

The ERG also asked the company to comment on the possibility of increased discontinuation rates, and consequent reduction of time on treatment, from the development of risk factors while on treatment with tofacitinib (for example, increased lipid levels or becoming a smoker). The ERG's advisers noted that many AS patients are overweight or obese which predisposes them to MACE and VTE events. The company presented data summarising findings for lipid levels, blood pressure and weight gain in study A3921120, up to 48 weeks follow-up. Of note, after an initial increase in cholesterol levels, these remained stable from week 16 to week 48. Mean blood pressure remained stable throughout the trial and body weight saw a mean increase of 2.2kg at 48 weeks follow-up. The company state there is insufficient data to make conclusion about the annual incidence rate (or similar metric) of acquiring a new risk cardiovascular factor among AS patients initiating tofacitinib, and how this would affect discontinuation rates.

The company also note that results from the NMAs versus adalimumab and secukinumab suggest no statistically significant difference. This analysis reports on a mixed population of bDMARD-experienced and naïve and uses data at 16-week follow-up from the tofacitinib A3921120 trial and adalimumab and secukinumab trials, and 12-week follow-up from the tofacitinib A3921119 trial. For MEASURE trials included in the NMA, longer-term follow-up data are available at 52-104 weeks, although these data are limited and are non-randomised past 16 weeks follow-up. Uncertainty remains around how the longer-term discontinuation rates for tofacitinib compares to other interventions and how this could impact time on treatment.

3.3.3 Network meta-analyses of safety and discontinuation outcomes

In their initial submission, the company did not conduct NMAs on AE outcomes for the comparison of tofacitinib to adalimumab but provided results for these analyses in their response to clarifications. Due to sparse data and the low number of studies in the NMA for SAEs only, an FE model was fit for the outcome. At the clarification stage the company were also asked to conduct an NMA of discontinuation rates due to AEs and SAEs from tofacitinib versus IL-17A inhibitors. Safety NMAs of tofacitinib against secukinumab in a mixed population (including both bDMARD-naïve and -experienced patients) were conducted as none of the included studies reported subgroup data based on prior biologic experience. COAST-W was not included in the networks for safety outcomes, therefore tofacitinib could not be compared to ixekizumab. Previous appraisals of secukinumab (TA407), ixekizumab (TA718) or TNF-alpha inhibitors (TA383) did not conduct safety NMAs.

The company was unable to fit a model for discontinuations due to AEs as all the adalimumab trials had zero discontinuations in the placebo arms. In their response to clarification question A22, the company conducted a frequentist NMA (adding a continuity correction to zero cell studies) which allowed estimation of relative effects for this outcome, although there was a lot of uncertainty in the estimates which are also slightly biased due to the addition of 0.5 to the zero cells. This is another situation where including data on other TNF-alpha inhibitors might have resulted in a more meaningful comparison. The company also fit a baseline-risk adjusted FE NMA model for overall discontinuation.

In their response to clarifications, the company also presented results for NMAs conducted on AE-related discontinuation and SAEs for the comparison of tofacitinib to secukinumab. The ERG agrees with all the models chosen by the company.

Results for the ERG-preferred models are presented in Table 8. CrIs for all the outcomes included the null effect, therefore there was insufficient evidence to suggest a difference in the incidence of AEs and discontinuations between tofacitinib and adalimumab, and tofacitinib and secukinumab. However, the ERG notes that the CrIs are all very wide, indicating large uncertainty in these comparisons.

Table 8. Results of ERG-preferred unadjusted models for AE outcomes (mixed population)

	NMA in Company Submission			NMA in Response to clarifications		
Outcome	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Adalimumab**	**Number of Studies**	**Selected Model**	**Tofacitinib vs. Secukinumab**
			OR (95% CrI)[a]			
Overall discontinuation	5	FE, BL-adj	[redacted]	Outcome not reported in the clarifications response		
AE-related discontinuation	5	FE, BL-adj	[redacted]	5	FE*	[redacted]
SAEs	4	FE	[redacted]	5	FE	[redacted]

[a] null effect is 0, * No RE models fit due to poor convergence

Abbreviations: AE: adverse events, BL-adj: baseline-risk adjusted, CrI: credible interval, FE: fixed effect, NMA: network meta-analysis, OR: odds ratio, RE: random effects-SAE: serious adverse events.

3.4 Summary of ERG's view

The clinical trial evidence submitted had sufficiently robust internal validity and its applicability to the NHS was acceptable. The company conducted NMAs to compare tofacitinib to adalimumab and to IL-17A inhibitors (i.e., secukinumab and ixekizumab) for efficacy and QoL outcomes. NMAs were conducted on subgroups based on previous bDMARD-experience. While evidence was available for both bDMARD-naïve and bDMARD-experienced patients for secukinumab, trials for adalimumab were only conducted in bDMARD-naïve patients and the only relevant trial for ixekizumab was conducted in bDMARD-experienced patients. For all efficacy and QoL outcomes, there was no evidence to suggest a difference in effects for tofacitinib compared to adalimumab, secukinumab, and ixekizumab. However, due to the sparsity of the networks especially for bDMARD-experienced patients, there was a high level of uncertainty in the estimates particularly for ASAS20, ASAS40, and BASDI 50 comparing tofacitinib to secukinumab and ixekizumab. The company fitted several different NMA models but overall, results were similar for all the models explored.

The company did not include all TNF-alpha inhibitors in the network comparing tofacitinib to adalimumab and did not consider fitting a class effect model. Therefore, it is unclear how tofacitinib compares to TNF-alpha inhibitors as a class.

Although the short-term safety and discontinuation data for tofacitinib appear similar to those for adalimumab, long-term safety data for AS patients are not available. Long-term randomised safety trial data from RA patients led the MHRA to issue a safety warning on the use of tofacitinib. The implications of this warning for AS patients means that support for the claim of clinical similarity with bDMARD comparators, in terms of safety, does not appear reasonable.

For AEs and discontinuations, NMAs comparing tofacitinib to adalimumab and secukinumab were conducted on mixed populations and were very uncertain.

4 SUMMARY OF THE ERG'S CRITIQUE OF COST EVIDENCE SUBMITTED

The appropriateness of assessing the cost-effectiveness of tofacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy (see Section B.3.9.2., CS) and safety (adherence and discontinuation, see Section B.3.10, CS, and response to clarification question 22b) of tofacitinib to at least one relevant comparator. Under the assumption that it is appropriate for this appraisal to proceed as a cost comparison FTA, the ERG seeks to identify the set of assumptions under which tofacitinib is likely to be cost saving or equivalent in cost to the selected comparator.

The ERG also highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of tofacitinib to at least one relevant comparator.

4.1 Company cost comparison

4.1.1 Summary of cost comparison

The company presented a cost comparison analysis between tofacitinib 5mg twice daily (BID) and adalimumab 40mg Q2W, henceforth referred to as tofacitinib and adalimumab, respectively. After the clarification stage, the company extended the cost comparison to include ixekizumab 80mg every four weeks (Q4W) (henceforth referred to as ixekizumab) and secukinumab 150mg and 300mg per month (secukinumab henceforth refers to secukinumab 150mg monthly, unless stated otherwise) as comparators. The company presented NMA results (response to clarification question A13) to support the assumption of similar efficacy and safety profile of tofacitinib and IL-17A inhibitors (see Section 3.2.3). The company considers adalimumab the most relevant comparator (see Section 2.1).

The costs included in the company's cost comparison are drug acquisition (Section B.4.2.3, CS), administration costs (Section B.4.2.4, CS), and monitoring costs (Section B.4.2.3, CS). Costs are estimated for time horizons of two, five and ten years. The company does not express a preference for any length of time horizon. Costs are reported separately for the first and subsequent years in the model. All costs are expressed in 2019/20 prices and undiscounted. The company considers that tofacitinib can be used as first or subsequent line of therapy, but does not present separate results for bDMARD-naïve and -experienced patient populations. A summary of costs applied in the cost comparison for the company base case analysis after clarification stage is presented in Table 9. A brief description of the parameterisation and assumptions of the cost comparison are presented in the following sub-sections.

As the company did not present clinical evidence to support the comparison with secukinumab 300mg (See Sections 2.1 and 3.2.3), and did not submit a version of the electronic model parameterised with this dosing schedule, the ERG focusses on the 150mg dosing schedule throughout the cost sections.

Table 9. Summary of costs in the cost comparison analysis

	Tofacitinib	Adalimumab	Ixekizumab	Secukinumab
Dose	5mg BID	40 mg Q2W	160 mg loading, then maintenance 80 mg Q4W	150mg per week for 5 doses, followed by: 150mg per month (secukinumab 150mg), or 300mg per month (secukinumab 300mg).
Mode of administration	Oral	SC injection	SC injection	SC injection
Drug acquisition unit cost	Xeljanz (5mg, 56 tablets): £690.03 (list price), [redacted] (PAS price)	Amgevita (40mg/0.8ml solution for injection, two pre-filled syringes,): £633.60	Taltz 80mg/1ml solution for injection pre-filled pens (pack of 1), £1,125.00 (list price)	Cosentyx 150 mg/1 ml - pre-filled disposable injection (pack of 2), £1,218.78 per pack (list price)
Annual drug acquisition cost	£9,001 (list price) [redacted] (PAS price)	£8,265	Year 1: £15,519 Subsequent years: £14,675	Year 1: £10,234* Subsequent years: £7,949*
Administration cost**	£0	£0	£0	£0
Monitoring costs (quarterly)	1st 12 weeks: £425.81 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04	1st 12 weeks: £423.27 Subsequent 12 weeks: £82.04

*For the secukinumab 150mg dose; **Originally included in the base case analysis and removed at clarification stage; BID, twice daily; Q2W, every 2 weeks; Q4W, every 4 weeks; PAS, patient access scheme; SC, subcutaneous.

4.1.1.1 Acquisition costs

Acquisition costs for tofacitinib are presented for the drug's list price and with a PAS, consisting of a simple discount of [redacted] on the list price from the British National Formulary (BNF) 2021.[26] The acquisition cost of adalimumab was based on the BNF 2021 list price of a biosimilar (Amgevita) corresponding to the lowest publicly available price of adalimumab. Biosimilars of adalimumab are available to the NHS at confidential framework prices provided by the Department of Health and Social Care Commercial Medicines Unit (CMU). The company did not present details on the acquisition costs of ixekizumab and secukinumab, but the costs used in the model match those in the BNF 2021.[26] There are also confidential PAS commercial arrangements in place for the use of ixekizumab and secukinumab in the NHS. The drug acquisition costs and results reported in this document do not reflect the framework prices of adalimumab biosimilar or the PAS commercial arrangements for ixekizumab and secukinumab; the PAS prices of ixekizumab and secukinumab are applied in a separate confidential appendix to this report. NICE did not make the confidential framework prices for adalimumab biosimilars available to the ERG; therefore, these could not be considered in the analysis presented in the confidential appendix. The annual and total drug acquisition costs in Table 9 assume the dosing schedules stipulated in the intervention and comparators' SmPCs. The company's analysis did not consider the effect of dose interruptions or adjustment upon acquisition costs.

4.1.1.2 Administration costs

SC administration of drugs is assumed to be undertaken by the patient following a one-off training by a nurse; only the cost of nurse time is included in the analysis, in line with TA383.[27] The unit cost of training corresponds to one hour of nurse time at a general practitioner (GP) practice (with qualifications, £42.00) according to Personal Social Services Research Unit, (PSSRU) 2020,[28] and in line with TA383.[11]

The company removed this cost from their updated base case analysis in response to clinical input provided by the ERG at the clarification stage.

4.1.1.3 Monitoring costs

Monitoring resource use (see Tables 32 and 33, CS, for details) is assumed to be the same for tofacitinib and the comparators, and is sourced from previous appraisals in AS;[2, 12, 27] with the exception of the inclusion of the additional assessment of lipid parameters performed eight weeks following initiation of tofacitinib therapy. Resource use and costs associated with monitoring are higher in the first year in the model for all treatments compared to subsequent years, due to more intensive monitoring in the initiation period (first 12 weeks of treatment) compared to the subsequent maintenance period.

4.1.1.4 Treatment discontinuation rates

Treatment discontinuation was not considered in the company's cost comparison analysis. The ERG requested that the cost-comparison be updated to allow the effect of treatment discontinuation to be explored, but the company declined this request, stating only that rates were similar between tofacitinib and the comparators.

4.1.1.5 Time horizon

The cost comparison did not present results over an explicitly defined time horizon. Instead, the company presented a comparison of costs over the first year of treatment, and a separate comparison of annual costs for any subsequent year. As the analysis did not account for treatment discontinuation, annual costs beyond the first year are constant. In response to a request by the ERG, the company also presented scenarios in which a number of time horizons up to a maximum of 10 years were considered.

4.1.1.6 Assumptions

The key assumptions underlying the cost comparison analysis are listed below:

- Adalimumab is the most relevant comparator in bDMARD-naïve and -experienced patient populations (see Sections 2.1 and 4.2.1); at the ERG request, the company also includes comparisons with ixekizumab and secukinumab.
- Equivalent effectiveness between tofacitinib and comparators means that it is appropriate to evaluate tofacitinib in the context of a cost-comparison FTA.
- Equivalent safety profile between intervention and comparators, leading to the exclusion from the comparison of any costs associated with the prevention and treatment of AEs.
- Comparable administration and monitoring costs for bDMARDs and tofacitinib in bDMARD-naïve and -experienced patient population, as no separate analyses are presented by patient population.
- No discontinuation or dose adjustments due to a loss of efficacy or AEs were considered. All patients are assumed to continue to maintenance treatment after the initial response assessment. Therefore, the cost-comparison does not account for the costs of subsequent treatments in initial non-responders or in those that discontinue after initial assessment.
- No specific time horizon duration was explicitly assumed, suggesting that differences between tofacitinib and the comparators scale linearly with each additional year due to no assumed discontinuation.

4.1.2 Results

The company presented mean undiscounted annual costs by category of cost for the full population in Table 104 (response to clarification question B3), and for a time horizon of 2, 5 and 10 years in Tables 109 to 111 (response to clarification question B7).

Under the company's assumptions, which include the PAS discount for tofacitinib and using the list prices for the comparators, tofacitinib is less costly than adalimumab, secukinumab and ixekizumab [redacted]. For subsequent years, tofacitinib is less costly than adalimumab, secukinumab and ixekizumab [redacted]. When considering the tofacitinib PAS price, tofacitinib is associated with [redacted] drug acquisition and administration costs, and higher monitoring costs compared to adalimumab, ixekizumab and secukinumab for time horizons of two, five and ten years. Total costs increase for all interventions with the increase of the time horizon.

The company presents a scenario analysis exploring the impact of including the costs of annual lipid monitoring for tofacitinib (Table 102, response to clarification question B2c). Results were not sensitive to the inclusion of this additional cost for tofacitinib, which resulted in an increase of approximately £3 per annum to the total costs of tofacitinib in subsequent years.

Subgroup analyses were considered unnecessary by the company, as the company did not expect differences in costs for tofacitinib and adalimumab in bDMARD-naïve and bDMARD-experienced patients. The only potential cost difference that is highlighted by the company refers to the administration cost of adalimumab for bDMARD-experienced, as patients may not require re-training to self-administer the drug; this cost was dismissed by the company as *"modest"*. Drug administration costs for subcutaneously delivered drugs were removed from the cost comparison at the clarification stage.

4.2 ERG critique of the company submission

The ERG validated the electronic model by auditing formulae, and cross-checking parameter values and results against the information provided by the company in the CS and response to clarification questions. The ERG detected an error on the dosing schedules of secukinumab and ixekizumab (see Section 4.2.5) in the electronic model submitted by the company at clarification stage, which was corrected. No further errors were detected in the economic model.

The ERG critique focuses on the following aspects of the cost comparison analysis:

- Population, treatment positioning and relevant comparators;
- Adverse events;

- Treatment adherence and discontinuation;
- Time horizon;
- Acquisition costs;
- Monitoring costs;
- Administration costs.

Following the critique, the ERG proposes an alternative base case analysis, exploring alternative assumptions to those used in the company analysis. The results of the ERG preferred base case are presented in a confidential appendix separate to this report.

The ERG notes that the cost-comparison model does not formally model response assessment at the end of the trial period, and therefore, costs are not estimated separately for patients who do not have a response to treatment at this time point, and move to the next line of treatment. Therefore, the differential costs between responders and non-responders to each of the comparators are not captured in the cost comparison model. This is a limitation of this analysis, but the ERG does not consider it to affect conclusions.

4.2.1 Population, treatment positioning and relevant comparators

The company positions tofacitinib at first or subsequent lines of treatment in the AS pathway (in line with its expected marketing authorisation for this condition), and provides the same cost comparison analysis to support its use in bDMARD-naïve and -experienced populations. The company considers adalimumab to be the most relevant comparator.

As detailed in Section 2.1, the ERG considers adalimumab is unlikely to be a relevant comparator for the cost comparison analysis; secukinumab is likely to be the most relevant comparator for bDMARD-experienced patients.

If tofacitinib is considered to constitute an additional line of therapy in AS (i.e., third-line or later), it will displace established clinical management without bDMARDs and therefore cannot be appraised in the context of a cost comparison FTA (see Section 2.2). Adding a line of treatment to the pathway has the potential to change downstream costs and HRQoL outcomes of managing the condition, and needs to be accounted for in a full cost-utility framework.

Another issue raised in Section 2.1 is that the population in which the clinical evidence provided by the company (critiqued in Section 3) was generated is wider than the population who will be eligible for treatment with tofacitinib in the UK according to the MHRA safety warning[1] and for the purpose of this appraisal. This introduces additional uncertainty around the equivalence assumption which underpins the appropriateness of the cost comparison.

The assumption of equivalent effectiveness and safety profile of tofacitinib and comparators is also particularly uncertain in the bDMARD-experienced population because the majority of patients treated with tofacitinib in clinical trials have not been previously treated with bDMARDs (Section 3.2.3).

4.2.2 Adverse events

As detailed in Sections 2.1 and 3.3, the ERG is concerned that the safety profile of tofacitinib is different from that of TNF-alpha inhibitors (and IL-17A inhibitors) due to the safety issues identified by regulatory agencies in regards to the use of tofacitinib and JAK inhibitors,[1, 19, 20], sparsity of long-term safety data, and concerns expressed by clinical advisers to the ERG.

At the clarification stage, the ERG requested the inclusion in the cost comparison analysis of costs associated with the prevention, diagnosis, management and treatment of AEs (see clarification question B2). The company chose to not include any AEs costs in their base case analysis, and justified their decision by stating that the safety data submitted in response to clarification questions A3-A5 (critiqued by the ERG in Section 3.3) does not support the existence of differences between tofacitinib and bDMARDs. In brief, the ERG critique of the evidence presented concludes it is insufficient to establish the equivalence of tofacitinib compared to bDMARDs, especially in terms of long-term safety (Section 3.3).

The ERG considers that, while the inclusion of AE costs in the cost comparison would have been appropriate, the issue remains that potential differences in the incidence of AEs between tofacitinib and adalimumab (as well as with IL-17A inhibitors) cannot be fully dealt with within the boundaries of a cost comparison FTA, and requires a full cost-effectiveness analysis to capture the impact on HRQoL due to the AEs and the consequences of discontinuing treatment (and switching to subsequent ones).

4.2.3 Treatment adherence and discontinuation

The company declined to present analyses considering the effect of treatment discontinuation upon ERG request, stating only that the discontinuation rates of tofacitinib and the three comparators in the NMAs were similar (see Section 3.2.3.4).

At present, the cost comparison can only provide the total costs per patient actively receiving treatment, rather than the ongoing costs of an average patient initiating treatment at the outset of the model. The consideration of discontinuation would have some informative value in a cost comparison context. Namely, it would allow internally consistent estimates of budget impact associated with tofacitinib across the population. That is, accounting for discontinuation would allow time on treatment to be explicitly modelled, which would inform an appropriate time horizon over which to

measure differences in accrued costs. The analysis would therefore give a more representative impression of the mean total costs of treatment and their magnitude relative to monitoring costs over time. However, estimates of real-world discontinuation rates remain themselves subject to uncertainty. As discussed in Section 4.2.4, additional monitoring costs associated with tofacitinib will accrue over the course of a typical patient's time on treatment. To understand the differences in monitoring costs between tofacitinib and the comparators, we must consider both the proportion of patients remaining on treatment and the timescales over which they are treated.

The ERG considers there to be a non-negligible risk that the long-term rates of treatment discontinuation experienced on tofacitinib will not be comparable to the chosen comparators. For the reasons discussed in Section 2.1, the restrictions issued by the MHRA may lead to additional sources of discontinuation relating to the development of risk factors for MACE, VTE, and malignancy, which were not captured in the syntheses of treatment discontinuation in the short-term. Discontinuation relating to shorter duration of treatment effect (i.e., potential loss of treatment effect) compared to bDMARDs has also not been adequately explored in the presented analyses. Therefore, there remains significant uncertainty regarding long-term discontinuation that cannot be captured in a cost comparison analysis. For example, in the event that discontinuation rates are indeed higher on tofacitinib, the cost comparison analysis is unable to characterise the impact on HRQoL and the cost of moving to a subsequent line of therapy.

4.2.4 Time horizon

The ERG requested that the cost comparison be updated to allow consideration of alternative time horizons, including a sensitivity analysis with a time horizon equal to estimated mean treatment duration. The company presented the results of sensitivity analyses using time horizons of two, five, and ten years. As treatment discontinuation was not considered in the updated model, the costs accrued annually do not change after the first year. The effect of increasing the time horizon is therefore illustrative only of budget impact per patient remaining on treatment.

The FTA cost comparison case requires accrued costs to be considered over a time horizon appropriately representing a typical course of treatment. The inclusion of additional monitoring costs for tofacitinib (See Section 4.2.6) would result in accrual of greater long-term costs to the NHS, and thus a time horizon representing at least the average course of treatment would be required to appropriately capture any important differences (see Section 4.2.6). The ERG therefore considers the most relevant time horizon to be reflective of the mean duration of treatment in practice. As this is uncertain, the ERG present base case results for a range of time horizons up to ten years.

4.2.5 Acquisition costs

The cost comparison model estimates acquisition costs in the first and subsequent years for tofacitinib and comparators. In the updated model submitted at the clarification stage by the company, the number of secukinumab doses at first and subsequent years was not calculated appropriately as it was assumed that this drug was administered in the maintenance period once every four weeks in contrast to once a month as per the dosing schedule recommended in the BNF.[26] Furthermore, the company also underestimated the number of doses administered for ixekizumab in the first year, by considering a longer interval between the initial loading dose and subsequent doses compared to what is recommended in the BNF (5 vs. 4 weeks).[26] The ERG corrected the dosing schedules for the IL-17A comparators in what is henceforth referred to as the ERG revised model; these are shown in Table 10 alongside those estimated by the company. The ERG preferred base case analysis applies the resource use described for the ERG revised model.

Table 10. Dosing schedules of secukinumab and ixekizumab in the models

Number of doses	Company's model*		ERG revised model*,**	
	1st year	Subsequent years	1st year	Subsequent years
Secukinumab	16.79	13.04	16.08	12.00
Ixekizumab	13.79	13.04	15.04	13.04

*a year is assumed to correspond to have 365.25 days on average
**on average a month is assumed to correspond to approximately 4.35 weeks

Prior to clarification, the company had assumed the year had a 365 days duration for the purpose of calculating acquisition costs of interventions in the cost-comparison. This was corrected at clarification stage to reflect that on average a year has a 365.25 days duration.

4.2.6 Monitoring costs

The ERG was initially unable to validate the unit costs applied by the company to value resource use associated with patient monitoring because the estimates used by the company did not match those in the source reference.[29] The company reported the version of the NHS reference costs[30] used in response to clarification questions, but updated the model in accordance to the source used by the ERG. The ERG notes that the magnitude of differences between the two sources are minute and unlikely to affect the results. The unit costs applied in the ERG revised model are presented in Table 12 (Appendix 2); these estimates also include other corrections detailed in Appendix 2. These corrections do not impact the results, as they apply to tofacitinib and comparators equally (with the exception of the baseline lipid profile assessment included for tofacitinib but not to comparators).

The ERG requested at the clarification stage that further monitoring costs were considered for patients treated with tofacitinib, namely a baseline risk assessment including lipid profiling, blood pressure

measurement, body weight measurement, and diabetes tests, and further annual lipid profile monitoring. The company stated that regular monitoring of cardiovascular risk factors is recommended for all patients with AS,[31] therefore it would affect both arms of the cost-comparison equally (response to clarification questions B1-2). A scenario analysis adding the cost of annual lipid profile monitoring (see Section 4.1.2, was presented to address this concern (Table 102, response to clarification question B2c), but it had a negligible impact on results.

The ERG notes that clinical guidance on monitoring cardiovascular risk factors in patients with AS predates the MHRA safety warning on tofacitinib.[1] Therefore, it is likely that the additional ongoing monitoring costs of tofacitinib, given the safety concerns, are not fully reflected in the model. Furthermore, there may be clinical variation on the level of additional resource use associated with monitoring patients on treatment with tofacitinib in light of safety concerns highlighted in Sections 2.1 and 3.3, so this represents an area of uncertainty. The costs associated with this will be accrued while patients are on treatment and, therefore, it is important that the time horizon of the cost-comparison covers the expected treatment duration. In the ERG preferred base case, annual lipid profile monitoring is included in the monitoring costs of tofacitinib, as a proxy for cardiovascular risk factors monitoring. The ERG notes that this is a small cost (£2.53 per year), and may not be reflective of costs to the NHS.

4.2.7 Administration costs

As previously discussed in Sections 2.1 and 4.2.1 the ERG considers tofacitinib to be most appropriately positioned in bDMARD-experienced patients. As such, the majority of patients initiating treatment on one of the comparator therapies will have already received training in the use of self-injecting SC administration devices at previous lines of therapy. Moreover, many companies provide this training free of cost to the NHS – particularly in the case of originator agents (e.g. Cosentyx and Taltz). Therefore, the ERG considers it appropriate that this cost is removed from the base case. The company agreed with the ERG's position and removed the one-off training cost from their updated base case analysis.

4.3 ERG preferred base case

The ERG base case analysis builds on the company's updated base case analysis submitted at clarification stage (see Table 103 and 104, response to clarification question B3); it differs from the company's by incorporating the following set of assumptions:

1. Monitoring of patients on treatment with tofacitinib requires baseline and annual lipid profile assessment in addition to the monitoring resource use associated with the comparators (see Section 4.2.6);

2. The unit cost of a TB test corresponds to £66.23 (see Section 4.2.6);
3. Dosing schedules of ixekizumab and secukinumab have been adjusted as described in Section 4.2.5.

Results of the base case analysis for the first and subsequent years, and for time horizons ranging from two to ten years, are presented in the confidential appendix to this report.

5 ERG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

5.1 Strengths

5.1.1 Clinical evidence:

- The clinical trial evidence submitted had sufficiently robust internal validity and its applicability to the NHS was acceptable.
- The evidence provided by the NMA results comparing tofacitinib to adalimumab and secukinumab in bDMARD-naïve populations and to secukinumab and ixekizumab in bDMARD-experienced populations, supports the assumption of equivalent efficacy against these comparators.

5.1.2 Economic evidence:

- The electronic model used to inform the cost-comparison analysis is simple and transparently presented, and no major errors were detected.
- The company updated the model at clarification stage to include alternative time horizon durations, which allowed the ERG to explore the impact of varying this parameter.

5.2 Weaknesses and areas of uncertainty

5.2.1 Clinical evidence:

- An important MHRA safety warning exists for tofacitinib. It is based on randomised safety trial evidence showing that patients on tofacitinib who have common cardiovascular and malignancy risk factors have an increased risk of MACE, malignancies, pulmonary embolism, deep vein thrombosis, VTE, serious infections and all-cause mortality. This means the assumption of safety equivalence is not reasonable.
- Considering the MHRA guidance on restricted use and tofacitinib's SmPC, the ERG estimates that at least half of the AS patients eligible for tofacitinib should only receive it if there are no suitable treatment alternatives, i.e. as a last line of therapy.

- Given these safety issues, the appropriate comparator for most patients would be established clinical management without biologics, though this is not listed in the NICE scope. This would not be a suitable comparator for the FTA process as it would not adequately represent the NICE recommended treatments as a whole in terms of cost and effects.
- Tofacitinib could be considered as a new line of therapy.
- The ERG's clinical advisers thought that the option of giving a treatment orally was unlikely to be an important advantage from the perspective of most AS patients, although it is very likely to be beneficial for the very few patients who are severely needle-phobic.
- Networks of evidence were sparse and did not include all TNF-alpha inhibitors, therefore it is unclear how tofacitinib compares to TNF-alpha inhibitors as a class.
- Relative effect estimates comparing tofacitinib to secukinumab and ixekizumab are uncertain.
- The assumption of equivalent efficacy and safety (adherence and discontinuation) between tofacitinib and the included comparators is highly uncertain. The sparsity of safety evidence on the use of tofacitinib in a bDMARD-experienced population is of particular concern.

5.2.2 Economic evidence:

- The appropriateness of assessing the cost-effectiveness of tofacitinib in the context of a cost comparison FTA relies on the validity of the assumption of equivalent efficacy and safety (adherence and discontinuation) of tofacitinib to at least one relevant comparator.
- The exclusion of the costs associated with AEs, particularly for longer-term AEs, from the cost comparison is an important area of uncertainty. If the safety profile of tofacitinib is worse than that of comparators, this exclusion would favour tofacitinib in the cost-comparison under consideration. Differences in the safety profile between interventions could have short-term costs and HRQoL impacts, and could also lead to complications and subsequent events with longer term impacts on health and health system costs (e.g., those associated with MACE and VTE). Differences in the safety profile between interventions could also impact on treatment discontinuation.
- Treatment discontinuation has not been formally modelled, and long-term discontinuation due to AEs or loss of tolerance is highly uncertain. Not accounting for treatment discontinuation introduces uncertainty on the costs of tofacitinib and comparators over time, and may impact on downstream costs and HRQoL outcomes.

- The relevant time horizon for the cost comparison analysis is uncertain, the ERG and company's base case results are sensitive to this parameter once the confidential prices of the comparators are considered.
- Costs associated with monitoring patients on treatment with tofacitinib are uncertain and are likely to be higher than what was considered in the cost comparison model, given safety concerns

on the use of this treatment raised by the MHRA. This uncertainty in the incremental monitoring costs associated with tofacitinib is further amplified by uncertainties surrounding treatment discontinuation and time horizon duration, as the proportion of patients who would remain on treatment with tofacitinib over time is unknown.

6 REFERENCES

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APPENDICES

APPENDIX 1: INCLUDED STUDIES

Table 11. Studies included in NMAs of each outcome for bDMARD-naïve and bDMARD-experienced populations

Outcomes	bDMARD-naïve‡			bDMARD-experienced		
	Tofacitinib	Adalimumab	Secukinumab	Tofacitinib	Secukinumab	Ixekizumab
ASAS20	A3921119 A3921120[a]	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a] MEASURE 4 [a] MEASURE 5 [a]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
ASAS40	A3921119 A3921120 [a]	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a] MEASURE 4 [a] MEASURE 5 [a]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
BASDAI50	A3921119 A3921120 [a]	COAST-V Huang 2014	---	A3921120 [b]	---	COAST-W
BASDAI CFB	A3921119† A3921120†	ATLAS COAST-V Huang 2014 M03-606	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST W
BASFI CFB	A3921119 A3921120 [a]	ATLAS COAST-V M03-606	---	A3921120 [b]	--	COAST-W
BASMI CFB	A3921119 A3921120 [a]	ATLAS Huang 2014 M03-606	---	---	--	--
ASDAS	---	---	---	A3921120 [b]	--	COAST-W
ASQoL CFB	A3921119 A3921120 [a]	ATLAS	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	---
SF-36v2 PCS CFB	A3921119 A3921120 [a]	ATLAS COAST-V Huang 2014	MEASURE 2 [a, c] MEASURE 4 [a, c] MEASURE 5 [a, c]	A3921120 [b]	MEASURE 2 [b] MEASURE 4 [b] MEASURE 5 [b]	COAST-W
SF-36v2 MCS CFB	A3921119 A3921120 [a]	ATLAS Huang 2014	---	---	---	---

[a] Subgroups of bDMARD-naïve patients from the study were used for the NMA. [b] Subgroups of bDMARD-experienced patients from the study were used for the NMA. [c] Sulfasalazine was treated as a placebo in the NMA. ‡ NMAs for the bDMARD-naïve were conducted in two separate analyses: tofacitinib vs. adalimumab and tofacitinib vs. secukinumab.

†There appeared to be a discrepancy in Table 44 of the clarification response, where it says that there were 102 patients in the tofacitinib arm and 105 patients in the placebo arm. The ERG assumes that the patient population (N) in trials A392119 and A3921120 were swapped, but it was unclear whether this was a typographical error or an error that was carried into the NMAs. The ERG was not able to check this in the files provided by the company in their clarification response.

APPENDIX 2: UPDATED MONITORING COSTS

In addition to updating the unit cost in accordance with the version identified by the ERG [NHS reference cost 2019/20], at clarification stage the company also corrected the unit cost for the TB test to reflect the use of an interferon gamma release assay (IGRA) According to clinical advice to the ERG the Heaf test is no longer used in clinical practice for latent TB detection. The company replaced the cost of the Heaf test with that of an IGRA test, the QuantiFERON – TB Gold-In Tube (QFT-GIT), and sourced it from a recent HTA report.[32] The ERG notes that according to the ERG clinical advisers there is one other test used in clinical practice, the T-SPOT.TB. Therefore, the ERG updated the cost of a TB test to the average cost of QFT-GIT and a T-SPOT.TB in the original source[33] used in the HTA report[32] uprated from 2009/10 to 2019/20 prices.[28]

The unit costs for antinuclear antibody testing and double stranded deoxyribonucleic acid (DNA) tests was also corrected to that of currency code DAPS06 (Other currencies),[29] which reflects the costs of an immunological assay.

Table 12. Monitoring unit costs in the ERG revised model

Item	Unit cost	Source
Full blood count	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).[29]
Erythrocyte sedimentation rate	£2.53	
Liver function test	£1.20	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS04 – clinical biochemistry).[29]
Urea and electrolytes	£1.20	
Chest X-Ray	£32.72	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Direct access plain film (Currency code DAPF).[29]
Tuberculosis test	£66.23	Pareek et al. (2013)[33] Average of Quantiferon – TB Gold-in Tube and T-SPOT.TB cost (£56.00) inflated from 2009/10 to 2019/20 prices based on the HCHS/NHSCII pay and prices inflation index in PSSRU Unit Costs of Health and Social Care 2020.[28]
Antinuclear antibody	£7.40	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS06 - immunology).[29]
Double-stranded DNA test	£7.40	
Specialist visit	£149.14*	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Consultant-led non-admitted face-to-face attendance, follow-up. (Currency code WF01A).[29]
Lipid parameters	£2.53	National Schedule of NHS Costs - Year 2019-2020 - NHS trusts and NHS foundation trusts. Directly Accessed Pathology Services. (Currency code DAPS05 - haematology).[29]

*Unit cost for Rheumatology visit; DNA, deoxyribonucleic acid; HCHS, hospital & community health services; NHS, National Health Service; NHSCII, NHS cost inflation index; PSSRU, Personal Social Services Research Unit.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Tofacitinib for treating active ankylosing spondylitis [ID3865]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 09 May 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Safety warnings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, section 1.1 Page 33, Section 3.4 Page 44, section 5.2.1 Incorrect conclusion on the safety profile of tofacitinib, that is not supported by evidence.	Page 8, section 1.1 The following sentences are misleading and should be corrected to reflect the evidence available on the safety of tofacitinib in the AS indication. *The safety data, therefore, do not appear to support the claim that tofacitinib's safety profile is similar to biological disease modifying anti-rheumatic drug (bDMARD) comparators.* The NMA results presented in the company submission and clarification response for tofacitinib vs placebo in the AS population is comparable to that observed for adalimumab vs placebo and secukinumab and ixekizumab vs placebo in the respective AS RCT populations. Therefore the sentence should be corrected to say: *The safety data, shows that tofacitinib's safety profile is similar to biological disease modifying anti-rheumatic drug (bDMARD) comparators if used in line with the risk minimisation plan outlined in the SmPC.* Page 33, Section 3.4 *The implications of this warning for AS patients means that support for the claim of clinical similarity with bDMARD comparators, in terms*	As detailed in clarification response A4, the safety warnings in the SmPC have been issued based on data from Study 1133, in a population with RA and high cardiovascular risk, however analyses of data from PsA, AS, PsO and UC populations, as well as in non-CV risk-enhanced RA population, have not shown an increased risk for tofacitinib therapy versus TNFi in for adverse events. In line with the SmPC, the benefit/risk ratio should be comparable when tofacitinib is used in line with the label and in accordance with risk minimisation materials. As explained in our response to clarification question A3, the MHRA issued the marketing authorisation for the AS indication months after the safety procedure has concluded and found the risk/benefit profile of tofacitinib satisfying. Therefore it did not consider it appropriate to restrict the marketing authorisation based on these risk factors.	Not a factual inaccuracy.

	of safety, does not appear reasonable. The sentence should be corrected to say: *The implications of this warning for AS patients means that support for the claim of clinical similarity with bDMARD comparators, in terms of safety, is reasonable if tofacitinib is used in line with the risk minimisation plan outlined in the SmPC.* Page 44, section 5.2.1 *This means the assumption of safety equivalence is not reasonable.* This sentence should be deleted.		

Issue 2 Risk factors in MHRA safety warnings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Arterial thromboembolism should not be listed as a risk factor, as ORAL Surveillance study did not show increased risk for this endpoint. Therefore, warnings on arterial thromboembolism are not included in the MHRA safety warnings or in tofacitinib SmPC and should be removed from the list in the ERG report.	Please remove arterial thromboembolism from the list on page 8, section 1.1; page 29, section 3.3.1 and page 44, section 5.2.1 *…increased risk of major adverse cardiovascular events (MACE), malignancies, pulmonary embolism, deep vein thrombosis, venous thromboembolism (VTE, serious infections and all-cause mortality in at-risk patients.*	It is incorrect to include arterial thromboembolism in the list of risk factors as it is not included in the MHRA safety warnings or in tofacitinib SmPC. Although the ORAL Surveillance study did look at this endpoint, the results did not show increased risk of arterial thromboembolism. Therefore, it should be removed from the lists provided in the ERG report at 3 occasions.	Deletions made as suggested.

Issue 3 Typo errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, 2nd paragraph Numbers for Study 1120 for compliance have been incorrectly reported in the ERG report.	*At 16-week follow-up, cumulative incidence of under-compliance is reported as* [redacted] *at 16-weeks follow-up* [redacted] *at 48-weeks follow-up. For trial A3921119 non-compliance (<80% compliance overall) was reported as* [redacted] *for 5mg tofacitinib (CSR Table 14.1.7.1).* The values have been incorrectly quoted from the CSR for Study 1120. Please correct them to say: *At 16-week follow-up, cumulative incidence of under-compliance is reported as* [redacted] *at 16-weeks follow-up and* [redacted] *at 48-weeks follow-up. For trial A3921119 non-compliance (<80% compliance overall) was reported as* [redacted] *for 5mg tofacitinib (CSR Table 14.1.7.1).* Besides, the following sentence should also be added for clarity: *However, non-compliance criterion (less than 80% compliance on 2 consecutive visits) was not met by any patient in either study 1120 or study 1119.*	Incorrect numbers have been quoted from the CSR, which should be corrected. Besides for clarity it should also be highlighted that the non-compliance criterion, which meant less than 80% compliance on 2 consecutive visits, as per study protocol, was not met in either of the studies, by any of the study participants.	Thank you for this. We have updated the data based on the 16-week analysis CSR to say the following: *At 16-week follow-up, cumulative incidence of under-compliance is reported as* [redacted] *at 16-weeks follow-up and* [redacted] *at 48-weeks follow-up (Table 14.4.1.9 CSR). For trial A3921119 non-compliance (<80% compliance overall) was reported as* [redacted]*, for 5mg tofacitinib (CSR Table 14.1.7.1).* We have not included the last statement suggested by the company (*However, non-compliance criterion (..) was not met by any patient in either study 1120 or study 1119*), as it does not relate to factual inaccuracy.
Page 32, Table 8	*Tofacitinib vs. Secukinumab, AE-related*	Please correct the typographical	Thank you for this. The

Incorrect lower bound is reported for credible interval.	*discontinuation OR (95% CrI* [redacted] The lower bound of CrI should be corrected to the following: Tofacitinib vs. Secukinumab, AE-related discontinuation OR (95% CrI): [redacted]	error.	correction has been made.
Page 32, Tale 8 Incorrect values reported for SAE	*Tofacitinib vs. Adalimumab, SAEs OR (95% CrI):* [redacted] The values should be corrected to the following, in line with Page 91 of the company clarification response. *Tofacitinib vs. Adalimumab, SAEs OR (95% CrI):* [redacted]	Please correct the typographical error.	Thank you, we have checked the results on pg. 91, of the response to clarification. However, it seems that the unadjusted results are reported in appendix 3 and are consistent with the numbers we have included in the ERG report. As such, these have not been amended.

Issue 4 Correction of references

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing reference on Page 30, 3rd paragraph	*The one study which did compare tofacitinib with TNF-alpha inhibitors was a non-randomised comparison in RA patients which reported similarities in MACE, malignancy, death, and VTE.*	Please provide reference for the study mentioned in the sentence. We believe the sentence must be referring to the Corrona RA registry, which 5 years results were published by Kremer et al. as referenced in the company clarification response for question A4. Kremer JM, Bingham CO, 3rd,	This reference has now been added

		Cappelli LC, Greenberg JD, Madsen AM, Geier J, et al. Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States-Based Rheumatoid Arthritis Registry. ACR Open Rheumatol. 2021;3(3):173-84.	
Page 30, 1st paragraph The results of ORAL Surveillance have now been published in NEJM	*Although the trial results have yet to be published in a peer-reviewed journal, they have been posted on the study's clinicaltrials.gov record.* Please amend this sentence to say: The results of the trial have been published by Ytterberg et al.. Ytterberg SR, Bhatt DL, Mikuls TR, et al.Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022 Jan 27;386(4):316-326	The trial results have now been published therefore correction of this sentence is needed.	Not a factual inaccuracy. The study was unpublished when the report was submitted.
Page 31, section 3.3.2, 1st paragraph	*Longer term data from an open-label study (ORAL Sequel long-term extension[23])) of tofacitinib (5mg and 10mg) for RA (including 4481 patients followed up to 114 weeks), suggests this could be notably higher, with 28% of patients discontinuing tofacitinib 5mg due to an AE.* The reference provided here is incorrect. The results of the ORAL Sequel long-term extension study have been published by Wollenhaupt et al. Wollenhaupt et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-	The reference should be amended to refer to the correct study.	Thank you for this. The reference has been updated.

	term extension study. Arthritis Research & Therapy (2019) 21:89 https://doi.org/10.1186/s13075-019-1866-2.		

Issue 5 Underestimation of IBD prevalence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, Table 1	*Patients with IBD (4%)* Figures in the literature show that this percentage can range from 4% to 16%. Please amend the heading to include the correct percentages found in the literature: *Patients with IBD (4-16%).*	The reference provided for Table 1 is de Winter et al. 2016, which reports 6.4% as pooled prevalence of IBD (Figure 3c of the publication). Besides, in the Background section of the publication, the authors report an estimated prevalence range of IBD to be 4-16% for patients with AS. The Patient/Carer Organisation Submissions for secukinumab (TA407) and ixekizumab (TA718) noted a prevalence of IBD in AS of 10%. The proposed amendment is aligned with above described prevalence figures. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-	The text on IBD in the de Winter et al 2016 paper contradicts Figure 3c in the same paper, mixing up the AS and nr-axSpA results. We agree that the Figure 3c results are more likely to be correct and have therefore amended Table 1 to read 6%.

		analysis. Arthritis Res Ther. 2016 Sep 1;18(1):196. doi: 10.1186/s13075-016-1093-z.	

(please cut and paste further tables as necessary)

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**

(Please add further lines to the table as necessary)